ASSESSMENT REPORT ON

HEXANE

FOR DEVELOPING AMBIENT AIR QUALITY OBJECTIVES

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HEXANE

FOR DEVELOPING AN AMBIENT AIR QUALITY OBJECTIVES

Prepared by
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IN CONJUNCTION WITH
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for
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FOREWORD

Alberta Environment maintains Ambient Air Quality Objectives[1] to support air quality management in Alberta. Alberta Environment currently has ambient objectives for more than thirty substances and five related parameters. These objectives are periodically updated and new objectives are developed as required.

With the assistance of the Clean Air Strategic Alliance, a multi-stakeholder workshop was held in October 2000 to set Alberta's priorities for the next three years. Based on those recommendations and the internally identified priority items by Alberta Environment, a three-year work plan ending March 31, 2004 was developed to review four existing objectives, create three new objectives for three families of substances, and adopt six new objectives from other jurisdictions.

In order to develop a new three-year work plan, a multi-stakeholder workshop was held in October 2004. This study was commissioned in preparation for the workshop to provide background information on alternative, science based, and cost effective methods for setting priorities.

This document is one of a series of documents that presents the scientific assessment for these adopted substances.

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Project Manager
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[1] **NOTE**: The *Environmental Protection and Enhancement Act*, Part 1, Section 14(1) refers to "ambient environmental quality objectives" and uses the term "guidelines" in Section 14(4) to refer to "procedures, practices and methods for monitoring, analysis and predictive assessment." For consistency with the *Act*, the historical term "ambient air quality guidelines" is being replaced by the term "ambient air quality objectives." This document was prepared as the change in usage was taking place. Consequently any occurrences of "air quality guideline" in an Alberta context should be read as "air quality objective."

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ACRONYMS, ABBREVIATIONS, AND DEFINITIONS

AAL	Allowable Ambient Level (Massachusetts) or Acceptable Ambient Level (North Carolina)
AAQC	Ambient Air Quality Criteria
AAS	Ambient Air Standard (Louisiana)
ACGIH	American Conference of Governmental Industrial Hygienists
AGC	Annual Guideline Concentration (New York State)
ANR	Vermont Agency of Natural Resources (Vermont)
ASIL	Acceptable Source Impact Level (Washington Department of Ecology)
ATC	Allowable Threshold Concentration – continuous exposure (daily lifetime) (Massachusetts DEP)
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
CalEPA	California Environmental Protection Agency
CAPCOA	California Air Pollution Control Officers Association
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CEIL	Ceiling Value
CEPA	Canadian Environmental Protection Act
DEC	Department of Environmental Conservation (*e.g.*, New York)
DENR	Department of Environment and Natural Resources (*e.g.*, North Carolina)
DEP	Department of Environmental Protection (*e.g.*, Massachusetts, New Jersey)
DES	Department of Environmental Services (*e.g.*, New Hampshire)
DEQ	Department of Environmental Quality (*e.g.*, Michigan, Louisiana, Oklahoma
DOE	Department of Environment or Department of Ecology (*e.g.*, Washington)
ENEV	Estimated No-Effects Value
EPA	Environmental Protection Agency (*e.g.*, Ohio)
ESL	Effects Screening Level
GLC	Ground Level Concentration
GV	Guideline Value
HAAS	Hazardous Ambient Air Standard
HEAST	Health Effects Assessment Summary Tables
HEC	Human Equivalent Concentration
HRV	Health Risk Value
IARC	International Agency for Research on Cancer
IHRV	Inhalation Risk Value
IRIS	Integrated Risk Information System
IRSL	Initial Risk Screening Level
ITSL	Interim Threshold Screening Level
LC50	Median Lethal Concentration
LD50	Median Lethal Dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
MAAC	Maximum Acceptable Ambient Air Concentration

MAAQC	Maximum Annual Air Quality Criteria
MAC	Maximum Acceptable Concentration
MACT	Maximum Achievable Control Technology
MAGLC	Maximum Acceptable Ground-Level Concentration
MDH	Minnesota Department of Health
MHRV	Multimedia Health Risk Value
MIC	Maximum Immission Concentration (Netherlands)
MPR	Maximum Permissible Risk Level
MRL	Minimal Risk Level
MTLC	Maximum Tolerable Level Concentration
NAAQO	National Ambient Air Quality Objective
NIEHS	National Institute of Environmental Health Sciences (USA)
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NPRI	National Pollutant Release Inventory
NRCC	Natural Resource Conservation Commission
NTP	National Toxicology Program (USA)
OEHHA	Office of Environmental Health Hazard Assessment (California EPA)
OEL	Occupational Exposure Limit
OMOE	Ontario Ministry of Environment
OSHA	Occupational Safety and Health Association
PEL	Permissible Exposure Limit
PM	Particulate Matter
POI	Point of Impingement
PSL	Priority Substance List
PSL1	First Priority Substances List (Canada)
PSL2	Second Priority Substances List (Canada)
RD50	Median Respiration Rate Decrease
REL	Either Reference Exposure Limit as used by the California EPA or Recommended Exposure Limit used by both NIOSH and ATSDR
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Netherlands Research for Man and Environment
RM	Risk Management
RTECS	Registry of Toxic Effects of Chemical Substances
SGC	Short-term Guideline Concentration
SRSL	Secondary Risk Screening Level
STEL	Short-term Exposure Limit
TAPG	Toxic Air Pollutant Guideline
T-BACT	Best Available Control Technology for Toxics
TC	Tolerable Concentration
TCA	Tolerable Air Concentration
TC01	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 1% increase in incidence or mortality due to tumours

TC05	Tumorigenic Concentration - the concentration of a contaminant in air generally associated with a 5% increase in incidence or mortality due to tumours
TD05	Tumorigenic Dose - the total intake of a contaminant generally associated with a 5% increase in incidence or mortality due to tumours
TEL	Threshold Effects Exposure Level
TLV	Threshold Limit Value
TNRCC	Texas Natural Resource Commission
TWA	Time-Weighted-Average
U.S. EPA	United States Environmental Protection Agency
WHO	World Health Organization

ppm	parts per million
ppb	parts per billion
mg	a milligram, one thousandth of a gram
µg	a microgram, one millionth of a gram
ng	a nanogram, one billionth of a gram

SUMMARY

Hexane is a colourless, clear, highly volatile and flammable liquid under standard conditions. The majority of n-hexane is obtained from the controlled fractional distillation of petroleum mixtures and other refinery-based processes. Commercial and laboratory grades of hexane are widely used as solvents and extractants in numerous industrial, commercial and domestic applications. n-Hexane is a naturally occurring component of crude oil and natural gas, and also may be a metabolic by-product produced by certain types of fungi, marine phytoplankton and terrestrial vegetation.

The majority of environmental releases of n-hexane are to air. In the atmosphere, n-hexane is expected to exist entirely in the vapour-phase. n-Hexane reacts readily with photochemically produced hydroxyl radicals in the atmosphere; this is believed to be the dominant fate process for n-hexane. The estimated half-life for this atmospheric reaction is 2.9 days.

The principal industrial sectors in Alberta that release n-hexane to air are food manufacturing (vegetable oil-based), oil and gas sector (including oil sands operations, and gas plants), and petroleum products manufacturing. For the majority of these facilities, fugitive emissions comprise the most significant portion of n-hexane emissions to air, although depending on the facility, stack emissions, releases during storage and handling, and other sources also can contribute appreciably to n-hexane air emissions.

Inhaled n-hexane is readily absorbed in the lungs, and is rapidly distributed to lipid-rich tissues within the body. The metabolism of n-hexane occurs in the liver, where it is metabolized by mixed function oxidases. Approximately 10 to 20% of absorbed n-hexane is excreted unchanged in exhaled air, with the remainder undergoing metabolism to mostly 2,5-hexanedione (2,5-HD) and 4,5-dihydroxy-2-hexanone in humans. Urinary excretion appears to be the most significant route of elimination for n-hexane metabolites.

Symptoms of acute human inhalation exposure to n-hexane include: vertigo, dizziness, lightheadedness, drowsiness, nausea, headache, eye and throat irritation, and paraesthesia. In general, n-hexane appears to be of relatively low acute toxicity to both humans and animals and high atmospheric concentrations are required to produce adverse health effects. Acute animal studies have demonstrated various adverse effects at concentrations above 2,000 ppm (7,040 mg/m^3).

It is well established that chronic human and animal exposure to n-hexane results primarily in motor and sensory peripheral neuropathy. In general, it can be estimated that workplace exposure to n-hexane at or above 500 ppm (1,760 mg/m^3) for several months may result in peripheral neuropathy in some individuals. Subchronic and chronic animal studies have reported NOAELs (No-Observable-Adverse-Effect-Levels) in the range of 100 to 3,000 ppm (352 to 10,560 mg/m^3), and LOAELs (Lowest-Observable-Adverse-Effect-Levels) in the range of 400 to 3,000 ppm (1,408 to 10,560 mg/m^3).

Current occupational exposure limits for n-hexane derived by ACGIH, NIOSH and OSHA are all based on human studies where peripheral neuropathy was the principal effect. Occupational polyneuropathy has been observed at air concentrations as low as 500 ppm (1760 mg/m^3).

No human studies were identified that investigated the reproductive or developmental effects of n-hexane or commercial hexane following inhalation exposure. Animal studies indicate that n-hexane can cause adverse effects in the testicular tissue of rats, but not mice. Reproductive or developmental toxicity has been reported to occur in rats at n-hexane concentrations >200 to 5,000 ppm (>704 to 17,600 mg/m^3). Commercial hexane studies with rats indicate lower developmental toxicity, with some studies reporting NOAELs between 900 and 3,000 ppm (3,169 and 10,560 mg/m^3). In mice, which are less sensitive, little or no reproductive or developmental toxicity has been reported at concentrations ranging from 200 to 9,000 ppm (704 to 31,680 mg/m^3). The weight of available evidence suggests that n-hexane does not appear to be teratogenic or cause serious developmental toxicity.

Studies with commercial hexane mixtures all show a lower degree of toxicity than studies with purified n-hexane.

The database on the genotoxicity potential of n-hexane is limited and equivocal. In a number of studies, rats appear susceptible to n-hexane-induced genotoxicity, whereas mice appear resistant. Bacterial assays have all shown negative results, and the few available Chinese hamster cell line studies have shown mixed results.

Although the scientific literature regarding the carcinogenic potential of n-hexane in humans is limited, no association has been found between the occurrence of cancer in humans and occupational exposure to n-hexane. Animal carcinogenicity studies with n-hexane are limited and inconclusive.

The majority of the existing air quality guidelines are based on either the U.S. EPA RfC of 0.2 mg/m^3, or the ACGIH TLV-TWA of 50 ppm (176 mg/m^3) (adjusted with various modifying and uncertainty factors). No current guidelines are based on odour considerations. Odour thresholds for n-hexane are highly variable and have been reported to range from 30 ppm to 248 ppm (106 to 873 mg/m^3). All existing air quality guidelines for n-hexane appear to be adequately protective of human health. In addition, given the available data on the environmental fate, transport and effects of n-hexane, n-hexane is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. While reaction of n-hexane with nitrogen oxides has been found to produce ozone precursors under controlled laboratory conditions, the smog-producing potential of n-hexane is considered very low relative to other alkanes or chlorinated VOCs. n-Hexane is noted to be one of the least photochemically reactive hydrocarbons.

1.0 INTRODUCTION

Alberta Environment (AENV) establishes Ambient Air Quality Objectives under Section 14 of the Environmental Protection and Enhancement Act (EPEA). These guidelines are part of the Alberta Air Quality Management System (AENV, 2000).

Ambient Air Quality Objectives (AAQO) provide the basis for determining whether or not ambient air quality is acceptable from a health perspective. For substances lacking Alberta objectives, the development of acceptable ambient air concentrations typically considers a number of factors, including physical-chemical properties, sources, effects on human and environmental health, air monitoring techniques and ambient air quality guidelines derived by other jurisdictions within Canada, the United States, various other countries, and multi-country organizations (*e.g.*, World Health Organization).

The main objective of this assessment report is to provide a review of scientific and technical information to assist in evaluating the basis and background for an Ambient Air Quality Objective for hexane. The following aspects were examined as part of this review:

- Physical and chemical properties
- Existing and potential natural and anthropogenic emissions sources in Alberta
- Effects on humans, animals and vegetation
- Monitoring techniques
- Ambient air quality guidelines in other Canadian jurisdictions, United States, European Union and Australia, and the basis for their development and use.

Key physical and chemical properties that govern the fate and behaviour of hexane in the environment are reviewed and presented in this assessment report. Existing and potential natural and anthropogenic sources of hexane air emissions in Alberta also are reviewed and presented in this report. This includes information obtained from Environment Canada's National Pollutant Release Inventory (NPRI) and the National Air Pollution Surveillance Network (NAPS Network).

Scientific information regarding the toxic effects of hexane on humans and animals is reported in a number of sources, including toxicological and epidemiological studies published in peer-reviewed journals and detailed regulatory agency reviews such as those published by the International Agency for Research on Cancer (IARC), World Health Organization (WHO), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Environmental Protection Agency's (U.S. EPA) Integrated Risk Information System (IRIS) and Toxicological Profiles, and Canadian Priority Substances List Reports under the Canadian Environmental Protection Act (CEPA 1999). There is a recent air quality guideline scientific support document for hexane from the Ontario Ministry of the Environment (OMOE, 2001) as well. These sources provide valuable information for understanding the potential human and environmental health effects of hexane. Key information from these sources regarding the effects of airborne concentrations of hexane on humans, animals, plants and the environment is summarized in this report.

Air monitoring and measuring techniques for hexane in air are well documented in the peer-reviewed scientific and regulatory agency literature. Several widely used and accepted air monitoring reference methods exist for hexane that have been developed, tested and reported by such agencies as U.S. EPA, U.S. National Institute of Occupational Safety and Health (NIOSH) and U.S. Occupational Safety and Health Administration (OSHA). These methods and techniques are summarized in this report.

2.0 GENERAL SUBSTANCE INFORMATION

Hexane is a colourless, clear, highly volatile liquid under standard conditions (ACGIH, 1998; WHO, 1991; Verschueren, 1983; HSDB, 2002). "Hexane" refers to the technical or commercial material that may contain a blend of n-hexane and a variety of other hydrocarbons (*e.g.,* toluene, acetone, acetone, methyl ethyl ketone, dichloromethane, trichloroethylene, pentane isomers, heptane isomers). These formulations may contain anywhere from 20 to 80% n-hexane (ATSDR, 1999). The term "normal" hexane or n-hexane refers to the specific linear unbranched hexane isomer. Other compounds are usually incorporated into the commercial grade formulations intentionally, as denaturants, and to discourage solvent abuse (*i.e.,* the intentional sniffing of hexane-containing products to get high) (ATSDR, 1999). The presence of these other compounds in many commercial grades of hexane has made it difficult to establish reliable odour thresholds for many products that contain n-hexane (ATSDR, 1999). Trace amounts of phthalate esters and organophosphorus compounds also have been reported to occur in commercial hexane mixtures (WHO, 1991).

For specialized oil extraction or laboratory uses, the purity of the hexane formulation may be in the range of 95 to 99% n-hexane; for uses where purity is not as important, commercial grade n-hexane mixtures can contain 20 to 80% n-hexane, with the remaining proportion of the mixture comprised of other C6 isomers, and other hydrocarbons.

This review focuses on the physical and chemical properties of n-hexane. The odour of n-hexane odour has been described as gasoline-like (HSDB, 2002) and slightly disagreeable (WHO, 1991). The compound is considered poorly soluble or insoluble in water but is miscible with most organic solvents and is very soluble in alcohol (WHO, 1991; NTP, 2001; ACGIH, 1998). n-Hexane reacts vigorously with oxidising compounds including liquid chlorine, concentrated oxygen, sodium hypochlorite and calcium hypochlorite. It is incompatible with dinitrogen tetraoxide and may attack some forms of plastic, rubber and coatings (NTP, 2001). n-Hexane is sensitive to light and prolonged exposure to heat (NTP, 2001). This chemical is a flammable liquid at room temperature and standard atmospheric pressure (WHO, 1991; NTP, 2001).

Table 1 provides a list of common synonyms, trade names, and identification numbers for n-hexane.

Table 1 Identification of n-Hexane

Property	Value
Formula	C_6H_{14}
Structure	
CAS Registry Number	110-54-3
RTECS Number	MN9275000
UN Number	UN1208
Common Synonyms	Dipropyl Hexyl hydride Normal hexane
Tradenames	Skellysolve B Gettysolve-B IMO 3.1 Standard Transportation No. 49 081 83 EC No. 601-007-01-4 NCI-C60571 ACX No. X1001498-5 RTK Substance No. 1340

Virtually all n-hexane is obtained from the controlled fractional distillation of petroleum mixtures and other refinery-based processes (Speight, 1991). Hexane also can be obtained from the remains of catalytic reformates after the removal of aromatics (WHO, 1991). Highly purified n-hexane can be produced from hexane mixtures by adsorption on molecular sieves (Dale and Drehman, 1985). As well, n-Hexane can be synthesized from sugar cane wastes using special catalysts (SUCRON, 1996); however, this method of synthesis is relatively new and the volume produced is very low (ATSDR, 1999).

Production levels and import/export information for n-hexane are poorly defined or outdated and very limited information appears to exist in the public domain (ATSDR, 1999).

Commercial and laboratory grades of hexane are widely used as solvents and extractants. The solvent and extractant applications are numerous and include: vegetable oil processing, coatings, paints, and adhesives and as a denaturant for alcohol (ACGIH, 1998). n-Hexane is used as a solvent, in low temperature thermometers, calibrations, polymerization reaction mediums, and as a paint thinner (HSDB, 2002; WHO, 1991; NTP, 2001). It is employed as a reaction medium, solvent or a feedstock in the manufacture of polyoleins, elastomers, pharmaceuticals, rubber tires, petrochemicals and cosmetics (HSDB, 2002; WHO, 1991). It is used also as a cleaning agent and degreaser in the textile, furniture, and leather industries. n-Hexane is a component of many fuels and other petroleum-based products, such as naphtha (ATSDR, 1999). It may be present in various inks, glues, sealants, propellants, hardening agents, lacquers, and adhesives. It

is a combustion product of polyvinyl chloride (ACGIH, 1998; HSDB, 2002; ATSDR, 1999). Pure n-hexane is widely used in laboratories as an extractant for nonpolar compounds and in calibrating instruments for analyses of volatile organic compounds (VOC) or total petroleum hydrocarbons (TPH) (Kanatharana *et al.*, 1993).

Limited information appears to exist in the literature concerning the disposal and environmental releases of n-hexane. Since it is highly flammable, n-hexane release and disposal is regulated in most countries, with disposals or releases being reported annually to national pollutant release inventories. Documented materials responsible for the release of n-hexane to the environment include printing pastes, paints, varnishes, adhesives and other coatings (HSDB, 2002). Hazardous waste disposal sites, landfills, petroleum refining operations and waste incinerators also are known to release n-hexane into the environment (HSDB, 2002).

2.1 Physical, Chemical and Biological Properties

The physical and chemical properties of n-hexane are summarized in Table 2.

Table 2 Physical and Chemical Properties of n-Hexane

Property	Value	Reference
Molecular Weight	86.18	ATSDR, 1999; HSDB, 2002; Clayton and Clayton, 1981
Physical State	Liquid	ATSDR, 1999
Melting Point	-94.3°C	Verschueren, 1983
	-95°C	WHO, 1991; NTP, 2001; ATSDR, 1999
	-95.3°C	Mackay *et al.*, 1993; RAIS, 2003
Boiling Point	68.7°C	Verschueren, 1983; RAIS, 2003
	68.74°C	Mackay *et al.*, 1993; Clayton and Clayton, 1981
	68.95°C	ACGIH, 1998
	69°C	WHO, 1991; NTP, 2001; Spicer *et al.*, 2002; ATSDR, 1999
Specific Gravity (liquid)	0.660 at 20°C	ACGIH, 1998; Verschueren, 1983; WHO, 1991; ATSDR, 1999
	0.664 at 25°C	Clayton and Clayton, 1981
	0.655 at 25°C	NTP, 2001
Specific Gravity (gas; air=1)	2.97	ACGIH, 1998; Clayton and Clayton, 1981
Vapour Pressure	16 kPa at 20°C	NTP, 2001; Verschueren, 1983
	20.0 kPa at 25°C	WHO, 1991; HSDB, 2002
	20.1 kPa at 25°C	Spicer *et al.*, 2002
	24 kPa at 25°C	NTP, 2001
	25.3 kPa at 30°C	Verschueren, 1983
Solubility in Water	76 mg/L at 20°C	ACGIH, 1998; Verschueren, 1983

Property	Value	Reference
	9.5 mg/L at 25°C	WHO, 1991; RAIS, 2003; ATSDR, 1999
Solubility	Very soluble in alcohol	ACGIH, 1998; Clayton and Clayton, 1981
	Miscible with most organic solvents	ACGIH, 1998; Clayton and Clayton, 1981; NTP, 2001; WHO, 1991
Henry's Law Constant	1.69 atm.m^3/mol at 25°C	ATSDR, 1999
	1.81 atm.m^3/mol at 25°C	HSDB, 2002
Octanol Water Partitioning Coefficient (log K_{ow})	3.29	ATSDR, 1999
	3.6	WHO, 1991
	3.9	RAIS, 2003; HSDB, 2002
Octanol Carbon Partitioning Coefficient (log K_{oc})	3.09 to 3.61	HSDB, 2002
Flash Point (closed cup)	-21.7°C	ACGIH, 1998; WHO, 1991; NTP, 2001; ATSDR, 1999
Explosive and Flammability Limits	1.1% to 7.5%	WHO, 1991
	1.2% to 7.5%	NTP, 2001
	1.18% to 7.8%	ACGIH, 1998; Clayton and Clayton, 1981
Autoignition Temperature	225°C	WHO, 1991; NTP, 2001; ATSDR, 1999
Odour Threshold	130 ppm	ACGIH, 1998; Amoore and Hautala, 1983
	65 ppm to 248 ppm	DHSS, 1997
	64.4 ppm to 245 ppm	Verschueren, 1983
	30 ppm to 245 ppm	van Gemert, 1999
Bioconcentration Factor in Fish	174 to 776	HSDB, 2002
	453	ATSDR, 1999
Conversion Factors for Vapour (at 25°C and 101.3 kPa)	1 ppm = 3.52 mg/m^3 1 mg/m^3 = 0.284 ppm	ACGIH, 1998; HSDB, 2002; Clayton and Clayton, 1981

2.2 Environmental Fate

The environmental fate of n-hexane is summarized in Table 3.

Table 3 **Environmental Fate of n-Hexane (based on ATSDR, 1999; Mackay *et al.*, 1993; HSDB, 2003)**

System	Fate	Half-life
Water	Loss by volatilisation and adsorption to sediment or suspended particulate matter; photolysis, hydrolysis, bioconcentration, and bioaccumulation are negligible	*Volatilisation*: 2.7 hours (model river) and 6.8 days (model lake)
Soil	Volatilisation and adsorption are the important environmental fate processes; photolysis and hydrolysis are negligible; biodegradation may occur; low to slight mobility; low potential for leaching	None identified.
Air	Exists solely as a vapour; degradation via reaction with hydroxyl radicals; photolysis is negligible	*Photochemical reactions with hydroxyl radicals*: 2.9 days

Given its Henry's Law Constant and high vapour pressure, the majority of environmental releases of n-hexane are to air. In the atmosphere, n-hexane is expected to exist entirely in the vapour-phase. Direct photolysis of n-hexane is not believed to be an important environmental fate process in the troposphere due to its inability to adsorb ultraviolet light (ATSDR, 1999). n-Hexane does not undergo hydrolysis in the atmosphere (ATSDR, 1999). n-Hexane reacts readily with photochemically produced hydroxyl radicals in the atmosphere; this is believed to be the dominant fate process for n-hexane. The estimated half-life for this atmospheric reaction is 2.9 days (HSDB, 2002). Experimental data suggest that night time reactions with nitrate radicals also may contribute to the atmospheric transformation of n-hexane, particularly in urban environments (HSDB, 2002). Reaction of n-hexane with nitrogen oxides has been found to produce ozone precursors under controlled laboratory conditions (Montgomery, 1991); however, the smog-producing potential of n-hexane is very low relative to other alkanes or chlorinated VOCs (Kopczynski *et al.*, 1972). n-Hexane is one of the least photochemically reactive hydrocarbons (Katagiri and Ohashi, 1975).

In water, volatilization is expected to be the most significant environmental fate process. In aquatic systems, n-hexane undergoes rapid volatilization with half-lives in a model river and a model lake reported to be 2.7 hours and 6.8 days, respectively (HSDB, 2002). Both photolysis and hydrolysis of n-hexane are expected to be negligible in water (ATSDR, 1999). Biodegradation of n-hexane may occur in water also. n-Hexane may also be physically removed from the water column via adsorption to organic matter contained in sediments and suspended particles (ATSDR, 1999). In groundwater, aerobic biodegradation is probably the most significant environmental fate process (*e.g.*, Rosenberg *et al.*, 1992). However, once introduced into groundwater, n-hexane may be fairly persistent as opportunities for biodegradation may be limited by hypoxic or anoxic conditions, or limited availability of nutrients such as nitrogen or phosphorus (ATSDR, 1999).

In soils and sediments, the dominant fate process for n-hexane, present at or near the surface, is believed to be volatilization, but no experimental information focusing directly on n-hexane appears to exist in the scientific literature (ATSDR, 1999). Hexane's estimated K_{oc} values suggest a moderate ability to sorb to soil particles. Given that its density is lower than that of water, and its low water solubility, n-hexane would occur as a light non-aqueous phase liquid (LNAPL). This suggests a low to moderate mobility and a low potential for leaching into subsurface soil, as n-hexane would tend to float on the top of the saturated zone of the water table (Feenstra *et al.*, 1991; Hunt *et al.*, 1988). In general, unless the n-hexane is present at depth within soils or sediments, volatilization is generally assumed to occur at a much more rapid rate than chemical or biochemical degradation processes. If introduced into deep soils and sediments, n-hexane can be persistent since opportunities for biodegradation may be limited by anoxic conditions and low availability of nutrients such as nitrogen and phosphorus.

Based on the relatively low log K_{ow} and log K_{oc} values (i.e., 3.3 to 3.9 and 3.09 to 3.61, respectively), significant bioconcentration and bioaccumulation in aquatic and terrestrial food chains are not anticipated (ATSDR, 1999; HSDB, 2002). A calculated bioconcentration factor (BCF) of 453 for a fathead minnow (ASTER, 1995) further suggests a low potential for n-hexane to bioconcentrate or bioaccumulate.

3.0 EMISSION SOURCES, INVENTORIES AND AMBIENT AIR CONCENTRATIONS

3.1 Natural Sources

n-Hexane is a naturally occurring component of crude oil and natural gas (ATSDR, 1999). Consequently, it is present in many fuels as a result of petroleum refining processes, and can be emitted into the atmosphere when hexane-containing fuel is combusted. It may be a metabolic by-product produced by certain types of fungi (Ahearn *et al.*, 1996). There is evidence (McKay *et al.*, 1996) that marine phytoplankton produce small amounts of n-hexane from the metabolism of polyunsaturated lipids in dissolved organic materials. In addition, very small amounts of n-hexane may be among the biogenic emissions from different types of terrestrial vegetation (Isidorov *et al.*, 1985; Winer *et al.*, 1992).

3.2 Anthropogenic Sources and Emission Inventory

3.2.1 Industrial

Production processes, as well as industrial, commercial and domestic sources and uses of n-hexane were described in Section 2.0.

A total of 89 industrial facilities in Alberta reported on-site releases of n-hexane to the 2001 National Pollutant Release Inventory (NPRI) database. Of the total reported environmental releases of n-hexane, the majority was released to the atmosphere; although, some facilities in Alberta also release n-hexane to land. For example, the Newalta Corporation in Elk Point, Alberta reported 0 tonnes released to air but 104.65 tonnes of n-hexane released to land (NPRI, 2001).

Table 4 provides total on-site releases for the top ten facilities in Alberta that release n-hexane to air, and Table 5 provides details on the air emissions for these facilities. The major sectors in Alberta that release n-hexane to air are food manufacturing (vegetable oil-based), the oil and gas sector (including oil sands operations and gas plants), and petroleum products manufacturing. For most of these facilities, fugitive emissions comprise the most significant portion of n-hexane emissions to air, although stack emissions, releases during storage and handling, and other sources also can contribute appreciably to n-hexane air emissions, depending on the facility (See Table 5).

Table 4 **Total On-site Releases (tonnes/year) of n-Hexane in Alberta (Ten Largest Contributors) According to NPRI, 2001**

NPRI ID	Facility Name	City	Total Releases (tonnes/year)			
			Air	Land	Water	Total
4829	Canbra Foods Ltd.	Lethbridge	305.57	0	0	305.57
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	249.27	0	0	249.27
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	112.12	0	0	112.12
5302	Newalta Corporation - Edmonton Process Facility	Edmonton	87.04	0	0	87.04
4591	ADM Agri-Industries Ltd. - ADM Lloydminster	Lloydminster	71.3	0	0	71.3
4468	CanAmera Foods - Fort Saskatchewan Plant	Fort Saskatchewan	36.69	0	0	36.69
3753	Rio Alto Exploration Ltd. - Gold Creek Gas Plant	Grande Prairie	25.76	0	0	25.76
3941	Novagas Canada Limited Partnership - Harmattan Gas Plant	Olds	23.02	0	0	23.02
0440	Pengrowth - Judy Creek Gas Conservation Plants	Swan Hills	16.36	0	0	16.36
3754	Paramount Resources Limited - Kaybob Gas Plant	Fox Creek	14.27	0	0	14.27

Table 5 Air Emissions of n-Hexane (tonnes/year) for Ten Largest Contributors in Alberta According to NPRI, 2001

NPRI ID	Facility Name	City	Air Emissions (tonnes/year)					
			Stack/ Point	Storage/ Handling	Fugitive	Spills	Other	Total
4829	Canbra Foods Ltd.	Lethbridge	0	0	305.57	0	0	305.57
2230	Suncor Energy Inc. - Suncor Energy Inc. Oil Sands	Fort McMurray	22.86	58.90	167.51	0	0	249.27
2274	Syncrude Canada Ltd. - Mildred Lake Plant Site	Fort McMurray	1.22	7.19	103.70	0	0	112.12
5302	Newalta Corporation - Edmonton Process Facility	Edmonton	0	0	0	0	87.04	87.04
4591	ADM Agri-Industries Ltd. - ADM Lloydminster	Lloydminster	9.90	0	61.40	0	0	71.3
4468	CanAmera Foods - Fort Saskatchewan Plant	Fort Saskatchewan	34.12	0	2.57	0	0	36.69
3753	Rio Alto Exploration Ltd. - Gold Creek Gas Plant	Grande Prairie	0	0.06	25.7	0	0	25.76
3941	Novagas Canada Limited Partnership - Harmattan Gas Plant	Olds	2.06	1.05	19.91	0	0	23.02
0440	Pengrowth - Judy Creek Gas Conservation Plants	Swan Hills	0.72	0.49	13.75	0	1.4	16.36
3754	Paramount Resources Limited - Kaybob Gas Plant	Fox Creek	1.36	0.57	12.34	0	0	14.27

3.3 Ambient Air Concentrations in Alberta

Alberta Environment has conducted a number of air quality monitoring surveys over the past several years in various regions of Alberta, a limited number of which have reported ambient air concentrations of n-hexane. For example, a VOC survey in the Fort Saskatchewan/Redwater area (AENV, 2003) conducted from May 2001 to February 2002 reported that one-hour average hexane air concentrations ranged from non-detectable to 1.99 $\mu g/m^3$ (average = 0.61 $\mu g/m^3$). A survey conducted in the Town of Banff in November 2002 reported one-hour average hexane concentrations on two sampling days of 0.87 and 1.23 $\mu g/m^3$ (AENV, 2002). These surveys utilized the mobile air monitoring laboratory, as well as stationary air samplers.

4.0 EFFECTS ON HUMANS AND ECOLOGICAL RECEPTORS

4.1 Humans and Experimental Animals

The following toxicological review of n-hexane centers on the inhalation route of exposure, as this is the predominant route of human exposure to n-hexane in air. Data on other exposure routes are included in this review only where considered relevant or where inhalation exposure data are lacking. Human studies are emphasized where sufficient data are available. However, relevant experimental animal studies are included where human data is either lacking or inadequate.

4.1.1 Overview of Toxicokinetics of n-Hexane

Absorption

In humans, roughly 20 to 30% of inhaled n-hexane is absorbed systemically (ATSDR, 1999). Absorption occurs via passive diffusion through epithelial cell membranes. In a study with six healthy male volunteers, Veulemans *et al.* (1982) reported that retention of n-hexane (as calculated from lung clearance and respiratory minute volume) was approximately 20 to 25% of the n-hexane in the inhaled air. Absorption rates of 0.84 mg/min at 102 ppm (359 mg/m^3) and 1.59 mg/min at 204 ppm (718 mg/m^3) were calculated. Physical exercise at 102 ppm caused a significant increase in lung clearance and at peak loads was more than twice the value at rest, resulting in an increase in the n-hexane absorption rate. When exposure ended, the lung clearance of n-hexane appeared to be biphasic, with a fast drop in the first 30 minutes followed by a slower drop for the remainder of the four-hour post-exposure observation period. Blood concentrations of n-hexane reached a steady state within 100 minutes and were stable until the end of exposure.

In a study of ten shoe factory workers (sex not specified, 18 to 30 years old), Mutti *et al.* (1984) reported that approximately 25% of inhaled n-hexane was retained in the alveoli. Absorption into the blood in relation to total respiratory uptake was about 17%, taking into account the retention coefficient and alveolar ventilation. The median time-weighted average n-hexane air concentration was 243 mg/m^3 (69 ppm); 2-methylpentane, 3-methylpentane, cyclohexane, and n-heptane also were known to be present in the workplace air.

The WHO (1991) noted that steady-state pulmonary retention (calculated by measuring the percentage of hexane in inhaled versus expired air) is generally reported to range from 15 to 30%, with no evidence of saturation at air concentrations up to 704 mg/m^3 (200 ppm). Pulmonary retention is noted to be greater in heavier individuals, and absorption increases slightly during exercise due to higher lung ventilation rates.

Distribution

The distribution of n-hexane is a function of its high lipid and very low water solubility; thus it preferentially distributes to lipid-rich tissues throughout the body. The preferential

distribution would be: body fat >>liver, brain, muscle > kidney, heart, lung > blood (ATSDR, 1999). Bus *et al.* (1981) found that n-hexane preferentially distributed to the sciatic nerve following either one- or five-day exposures to n-hexane at 1,000 ppm (3,520 mg/m^3) for six hours a day. n-Hexane also was detected in the kidney, liver, brain, and blood in this study.

Placental transfer of n-hexane, as well as the n-hexane metabolites, 2-hexanone and 2,5-hexanedione has been demonstrated in rats (Bus *et al.*, 1979). However, no preferential distribution to the fetus was observed for either n-hexane or its metabolites. Bus *et al.* (1979) also found no significant difference between n-hexane blood concentrations in mothers and total foetal concentrations after exposure during pregnancy. This study indicates that transfer of n-hexane across the placenta can occur in humans. A calculated milk/blood partition coefficient of 2.10 (Fisher *et al.*, 1997) suggests that n-hexane or its metabolites would transfer to breast milk. As it undergoes relatively rapid metabolism, n-hexane does not tend to be stored in body fat or other tissues to a significant extent (ATSDR, 1999). Thus, there is unlikely to be significant mobilization of stored n-hexane during weight loss, pregnancy or lactation. Based on testicular effects observed in male rats after drinking water exposure to 2,5-hexanedione, there appears to be transfer of this metabolite to germ cells (ATSDR, 1999).

n-Hexane appears to rapidly reach steady state once absorbed into the body. Veulemans *et al.* (1982) reported that blood levels of n-hexane reached steady state within 100 minutes. In rats exposed to up to 10,000 ppm (35,200 mg/m^3) n-hexane for six hours, steady state was reached in all tissues within two hours (Baker and Rickert, 1981).

Metabolism

The metabolism of n-hexane occurs in the liver, where it is metabolized by mixed function oxidases. The initial reaction is oxidation by cytochrome P-450 isozymes to hexanols, predominantly 2-hexanol. Further reactions then convert 2-hexanol to 2-hexanone, 2,5-hexanediol, 5-hydroxy-2-hexanone, 4,5-dihydroxy-2-hexanone and the potent neurotoxicant 2,5-hexanedione (ATSDR, 1999; WHO, 1991). Hydroxylation at the 1- and 3- positions can be considered detoxification pathways; hydroxylation at the 2-position is considered a bioactivation pathway (ATSDR, 1999).

Crosbie *et al.* (1997) reported that the tissue type with the highest n-hexane metabolism activity (for production of 2-hexanol) was the liver, followed by lung (which possesses roughly 25% of liver activity), muscle and brain. Metabolic activity in muscle and brain tissue is very low compared to the liver.

Approximately 10 to 20% of n-hexane absorbed by inhalation is excreted unchanged in exhaled air, with the remainder undergoing metabolism (ATSDR, 1999).

In rats, the major urinary metabolite recovered is 2-hexanol (Fedtke and Bolt, 1987) while in humans the major urinary metabolite is 2,5-hexanedione (Perbellini *et al.*, 1981). Concentration time curves for n-hexane in a closed exposure system indicated that metabolism in rats was proportional to air concentrations up to around 300 ppm (1,056

mg/m^3) (Filser *et al.*, 1987). Above 300 ppm, metabolism was non-linear, and appeared to be saturated at concentrations greater than or equal to 3,000 ppm (10,560 mg/m^3).

It is important to recognize that a large proportion of the 2,5-hexanedione detected in human urine following n-hexane exposure is an artefact that results from treatment of urine with acid to hydrolyze urinary conjugates (Fedtke and Bolt, 1987). For example, when urine from a male volunteer exposed to 217 ppm (764 mg/m^3) n-hexane for four hours was hydrolyzed enzymatically with β-glucuronidase, excretion of 4,5-dihydroxy-2-hexanone was approximately four times higher than that of 2,5-hexanedione. When the urine was hydrolyzed with acid instead, 4,5-dihydroxy-2-hexanone was not detected at all, and the amount of 2,5-hexanedione in the urine increased substantially. The 4,5-dihydroxy-2-hexanone had been converted to 2,5-hexanedione by the acid treatment. This was confirmed by calculations indicating that the fraction of 2,5-hexanedione determined after complete acid hydrolysis minus the 2,5-hexanedione originally present, was equal to the 4,5-dihydroxy-2-hexanone concentration (Fedtke and Bolt, 1987). Only minor amounts of 2-hexanol were reported in the urine of this volunteer.

Small amounts of n-hexane may be produced endogenously by lipid peroxidation (Filser *et al.*, 1983).

In a study with pregnant rats exposed to 1,000 ppm (3,520 mg/m^3) n-hexane, Bus *et al.* (1979) reported that n-hexane and the metabolite, 2-hexanone were rapidly eliminated from both maternal tissues and the fetus, with low to non-detectable concentrations by eight hours post-exposure. The metabolite, 2,5-hexanedione exhibited a slower elimination rate than n-hexane and 2-hexanone. It was reported to be non-detectable in blood or tissues 24 hours after exposure. The half-life of 2,5-hexanedione in maternal blood was higher than the half-life for either n-hexane or 2-hexanone (3.9 hours versus 1.24 and 0.99 hours, respectively).

Given its non-specific biotransformation once absorbed into the body, n-hexane has a high potential for interaction with other organic chemicals, particu'arly other organic solvents that are metabolized by mixed function oxidase enzymes. A large number of studies have demonstrated that co-exposure to other chemicals can influence the metabolism of n-hexane. Metabolic and toxicological interactions with n-hexane have been reported for: methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), acetone, xylenes, toluene, and trichlorethylene (Ichihara *et al.*, 1998; Van Engelen *et al.*, 1997; Robertson *et al.*, 1989; Baelum *et al.*, 1998; Cardona *et al.*, 1996; Ladefoged *et al.*, 1989, 1994; Nylen *et al.*, 1994; Pryor and Rebert, 1992; Nylen and Hagman, 1994; Nylen *et al.*, 1989; Yu *et al.*, 2002). These interactions have resulted in mixed outcomes for n-hexane toxicity; in some studies, n-hexane toxicity was potentiated, while in others it was reduced by co-exposure. For example, acetone, MIBK, and MEK potentiate the toxicity of n-hexane by increasing the amount of 2,5-hexanedione, while xylene and toluene have been reported to reduce the toxicity (ATSDR, 1999; OEHHA, 2003; Yu *et al.*, 2002; WHO, 1991). Recently, zinc also has been found to interact with n-hexane. Mateus *et al.* (2002) demonstrated a significant decrease in neurobehavioral dysfunction in rats co-exposed to 2,5-hexanedione and zinc acetate. The results suggest that zinc is a potential chemo-protector against 2,5-hexanedione neurotoxicity.

Elimination and Excretion

As mentioned, approximately 10 to 20% of absorbed n-hexane is excreted unchanged in exhaled air, with the remainder undergoing metabolism to mostly 2,5-hexanedione and 4,5-dihydroxy-2-hexanone in humans. In a study of workers exposed to n-hexane, the post-exposure alveolar excretion of n-hexane was about 10% of the total uptake, and occurred in two phases: a fast phase with a half-life of 11 minutes and a slow phase with a half-life of around 99 minutes (Mutti *et al.*, 1984).

2,5-hexanedione is the major metabolite recovered in human urine. However, as n-hexane metabolites in the urine and in exhaled air do not account for total intake, it is believed that some metabolites of n-hexane may enter intermediary metabolism in the body (ATSDR, 1999). Radiolabelled carbon dioxide was detected in the exhaled air after laboratory animal exposure to [^{14}C] n-hexane (Bus *et al.*, 1982), indicating that intermediary metabolism of some n-hexane metabolites occurred.

Urinary excretion appears to be the most significant route of elimination for n-hexane metabolites. Excretion in the urine is rapid and biphasic, and half-lives of excretion have been estimated at roughly 13 to 14 hours (Perbellini *et al.*, 1981; 1986; Bus *et al.*, 1982).

Physiologically-Based Pharmacokinetic (PBPK) Models

Two PBPK models for n-hexane were identified in the scientific literature. The Perbellini model (Perbellini *et al.*, 1986; 1990) is an eight-compartment model that simulates the absorption, distribution, biotransformation, and excretion of n-hexane during inhalation exposure. The excretion kinetics of 2,5-hexanedione also are simulated. Fisher *et al.* (1997) developed a model describing the transfer of n-hexane from a mother to a nursing infant during lactation.

The Perbellini model for n-hexane is the only validated PBPK model identified in the peer reviewed literature. The Fisher model has not been validated. Further information on these models is provided in the original papers, as well as in ATSDR (1999).

Mechanism of Toxic Action

The primary target for n-hexane in humans is the peripheral nervous system as it is well established that the most commonly reported toxic effect of n-hexane exposure in humans is peripheral neuropathy (both sensory and motor). Effects also have been noted on the central nervous system (WHO, 1991). In rats, the main target of n-hexane toxicity is the peripheral and central nervous system, and male reproductive tissues. Effects on respiratory tissues have been observed in mice and rabbit studies (WHO, 1991; ATSDR, 1999).

The neurotoxicity of n-hexane is widely believed to ultimately result from the effects of the principal metabolite, 2,5-hexanedione, on peripheral nerves, although other

metabolites of n-hexane have been reported to cause neurotoxicity also (*e.g.*, 2,5-hexanediol, 2-hexanone) (WHO, 1991).

In vitro experiments have shown that 2,5-hexanedione reacts with lysine side-chain amino groups in proteins to form pyrroles, and that these modified proteins can undergo secondary reactions to yield oxidized and polymeric products (DeCaprio *et al.*, 1982; Graham *et al.*, 1982). *In vivo* evidence of these reactions comes from a study in which oral administration of 2,5-hexanedione produced 2,5-dimethylpyrrole adducts in serum and axonal cytoskeletal proteins (DeCaprio and O'Neill, 1985).

St. Clair *et al.* (1988) tested a series of 2,5-hexanedione analogues for their ability to produce neurotoxicity in rats, and found that only those with the 2,5 gamma spacing were neurotoxic, and that potency correlated with the rate constant for pyrrole formation. The role of oxidation of the pyrrole adduct in the development of neurotoxicity was demonstrated with another 2,5-hexanedione analogue which could form pyrroles but was resistant to oxidation. This analogue (3-acetyl-2,5-hexanedione) caused pyrrolidation of proteins *in vivo*, but did not cause neurotoxicity.

As the maintenance of the axon depends on the transport of cellular components from the neuronal cell body, the effect of 2,5-hexanedione on axonal transport has been investigated (Pyle *et al.*, 1993; Graham *et al.*, 1995). Treatment with 2,5-hexanedione resulted in accelerated rates of transport that persisted after treatment ended. Increased rates of axonal transport may reflect a reparative response after neuronal injury (Graham *et al.*, 1995).

The sequence of events involved in neurofilament cross-linking, neurofilament accumulation, axonal swellings, and ultimate axonal degeneration that is observed in n-hexane neurotoxicity also has been investigated, but further study is needed to better understand the roles of these processes in causing neurotoxicity (Graham *et al.*, 1995).

Abnormal accumulations of neurofilaments (NF) and NF-immunoreactive products in nerve fibers and increased numbers of fibrils in endoneurial endothelial cells of the sural nerve have been observed in subjects with severe n-hexane induced peripheral neuropathy from glue sniffing (Jauma *et al.*, 1998). The authors suggest that high doses of n-hexane cause a diffuse intermediate NF disorder in a similar form as occurs in giant axonal neuropathy.

The rat is the major animal model system for human n-hexane neurotoxicity, as the inhalation of n-hexane in this species produces similar clinical and histopathological effects to those seen in exposed workers (ATSDR, 1999). However, the toxicokinetics in rats are somewhat different than in humans (*e.g.*, less 2,5-hexanedione and more 2-hexanol are produced as urinary metabolites (Fedtke and Bolt, 1987; Frontali *et al.*, 1981). Mice do not develop clinical signs of neurotoxicity after exposure to n-hexane, although histopathological changes in neurons (paranodal axonal swellings) have been observed (Dunnick *et al.*, 1989; NTP, 1991). Rabbits exposed to 3,000 ppm (10,560 mg/m^3) n-hexane showed no evidence of neurotoxicity in this species (Lungarella *et al.*, 1984).

As mentioned in the discussion of metabolism, n-hexane has a high potential for interaction with other organic solvents. These interactions have resulted in mixed outcomes for n-hexane toxicity, potentiating toxicity in some studies, and reducing toxicity in others.

Biomarkers

The most useful biomarker of n-hexane inhalation exposure is urinary 2,5-hexanedione. The quantity of this metabolite in urine is well correlated with airborne concentrations of n-hexane in workplace air (Mutti *et al.*, 1984). Mayans *et al.* (2002) also found a strong correlation between exposure to n-hexane and urinary 2,5-hexanedione levels and suggested that urinary 2,5-HD should be used as a biomarker of occupational exposure to n-hexane.

However, as n-hexane and its metabolites are cleared from the body within a few days, urinary 2,5-hexanedione is indicative of recent exposure only. In addition, another relatively common solvent, 2-hexanone, also gets metabolized to 2,5-hexanedione; thus, exposure to this chemical would have to be ruled out to confirm that urinary 2,5-hexanedione is due to n-hexane exposure only. As mentioned earlier, 2-hexanone is also a minor metabolite of n-hexane, but is only present in small quantities in human urine (Fedtke and Bolt, 1987).

Again, a large proportion of the 2,5-hexanedione detected in human urine following n-hexane exposure is an artefact that results from the acid hydrolysis of the metabolite, 4,5-dihydroxy-2-hexanone (Fedtke and Bolt, 1987). However, the acidification of urine samples is a common laboratory procedure that is performed to hydrolyze various urinary conjugates that can interfere with chemical analysis of the urine (ATSDR, 1999). Prieto *et al.* (2003) found that free urinary 2,5-hexanedione (which does not include acid-hydrolyzed 4,5-dihydroxy-2-hexanone) is a better indicator for evaluating risk from n-hexane exposure, since the concentration of free 2,5-hexanedione is strongly correlated to the endpoint of neurotoxicity. However, analyses of the relationship between the levels of atmospheric n-hexane and those of metabolites in urine show a greater correlation for total 2,5-hexanedione (which includes acid-hydrolyzed 4,5-dihydroxy-2-hexanone) than for free 2,5-hexanedione.

ACGIH (2004) currently assigns a biological exposure index (BEI) of 5 mg/g creatinine for 2,5-hexanedione in urine. The BEI is a reference value intended as a guideline for the evaluation of potential health hazards in the workplace.

Mateus *et al.* (2002) noted that pyrrole derivatives may constitute strong predictive biomarkers of 2,5-hexanedione exposure and could be used as a complementary tool to characterize its neurotoxic effects. The potential use of pyrrole derivatives as biomarkers reflects observations that pyrrolidation of proteins (particularly neuronal axon proteins) appears to be a necessary step in n-hexane neurotoxicity (Graham *et al.*1995). Pyrrolidated proteins in rat hair have been measured after intraperitoneal administration of 2,5-hexanedione (Johnson *et al.*, 1995). The presence of pyrrolidated proteins may

eventually be used as a biomarker for past exposures to n -hexane in humans (ATSDR, 1999). Anthony *et al.* (1983) suggested that a sensitive and rapid biomarker for 2,5-hexanedione exposure is the crosslinking of erythrocyte spectrin, where the altered migration of crosslinked spectrin is easily observable in polyacrylamide gels. However, further research is needed to determine whether exposure to n-hexane also results in adduct formation and/or crosslinking of spectrin via its metabolism to 2,5-hexanedione (ATSDR, 1999).

There are currently no sensitive biomarkers of effects associated with exposure to n-hexane, although this is an active area of research. Electroneuromyographic testing for detection of nerve conduction abnormalities, and pyrrolidation and crosslinking of proteins show promise as potential biomarkers (ATSDR, 1999).

4.1.2 Acute Toxicity

Symptoms of acute human inhalation exposure to n-hexane include: vertigo, dizziness, light-headedness, drowsiness, nausea, headache, eye and throat irritation, and paraesthesia. High intensity short-term exposure to n-hexane, such as that observed with glue sniffers or certain occupational situations may produce severe neuropathy that manifests as partial conduction blocks (Pastore *et al.*, 2002). Kuwabara *et al.* (1999) studied n-hexane neuropathy caused by addictive inhalation in four patients. The neurological manifestations were characterized by predominantly motor polyneuropathy with disease progression despite discontinuance of exposure. Neuropathological symptoms were similar to those reported in industrial exposures, although of greater severity; anorexia and body weight loss were reported as well. Electrophysiological studies showed that conduction block was a frequent finding.

In general, n-hexane appears to be of relatively low acute toxicity to both humans and animals and high atmospheric concentrations are required to produce adverse health effects.

Ten human volunteers of mixed sexes exposed to hexane (purity and isomer composition were not specified) for three to five minutes in an inhalation chamber displayed no irritation of the eyes, nose, or throat up to the highest concentration tested (500 ppm; 1,760 mg/m^3) (Nelson *et al.*, 1943).

Inhalation of 17,600 mg/m^3 (5,000 ppm) by human volunteers for ten minutes resulted in vertigo and giddiness. These symptoms were not reported at 7,040 mg/m^3 (2,000 ppm) for the same duration (Patty and Yant, 1929). Occupational exposures to hexane concentrations of 3,520 to 89,760 mg/m^3 (1,000 to 25,500 ppm) for periods of 30 to 60 minutes produced drowsiness (Yamada, 1967). Drinker *et al.* (1943) reported slight nausea, headache, and eye and throat irritation following human exposure to 1,400 to 1,500 ppm (4,928 to 5,280 mg/m^3) n-hexane.

Two workers at a hexane extraction facility reported transient paraesthesia following high intensity acute exposure to hexane (NIOSH, 1981). The predominant health complaint was temporary episodes of light-headedness and dizziness. The maximum time-weighted

average (eight hours) hexane concentration at this facility was reported to be 92 mg/m^3 (26 ppm). In workers at a soybean extraction facility exposed to hexane vapours, the major reported symptoms were dizziness, giddiness, and light-headedness (NIOSH, 1983). Headache and weakness also were reported in roughly half the cases. In addition, operators had a higher incidence of sleepiness (41%) than did maintenance workers (0%). Hexane exposure concentrations in personal breathing zones ranged from 15.5 to 46.5 mg/m^3 (4.4 to 13.2 ppm), but leaks from some process equipment may have led to higher levels of acute exposure in some workers.

Symptoms of n-hexane acute toxicity in experimental animals include: various manifestations of neurotoxicity, sensory and motor peripheral neuropathy, as well as respiratory effects and testicular lesions in some studies. Overall, n-hexane appears to be of relatively low acute toxicity in experimental animals, and high atmospheric concentrations are required to produce adverse health effects.

A one-hour LC50[2] value of 77,000 ppm (271,040 mg/m^3) was reported for male adult Fischer 344 rats (Pryor *et al.*, 1982). These rats also showed myoclonic seizures and ataxia at concentrations above 48,000 ppm (168,960 mg/m^3). No acute behavioural effects were noted in rats exposed to 24,000 ppm (84,480 mg/m^3) for ten minutes (Pryor *et al.*, 1982). When F344 rats were exposed for 24 hours per day, 5 days per week, for 11 weeks to 95% pure n-hexane at 1,000 ppm (3,520 mg/m^3), there was inhibition of body weight gain, which recovered somewhat after the exposure period (Pryor *et al.*, 1982). Other effects noted were inhibition of spontaneous motor activity, diminished hind limb grip strength, decreased multi-sensory conditioned avoidance response and pole-climbing ability by week 8 (recovery occurred post-exposure).

An LC50 of 73,680 ppm (259,354 mg/m^3) was reported in male Long-Evans rats exposed for four hours to a C-6 aliphatic hydrocarbon fraction containing only n-hexane and its isomers (Hine and Zuidema, 1970). All deaths occurred during the four-hour exposure period with the exception of one rat exposed to 81,800 ppm (287,936 mg/m^3), which had convulsions during and after exposure and died six days post-exposure. Rats that survived showed in-coordination, prostration, or were comatose during exposure but recovered within a few hours after removal from the test chamber. It was noted that the concentrations resulting in deaths were well above the reported lower explosive limit for n-hexane vapour of approximately 11,000 ppm (38,720 mg/m^3).

Sprague-Dawley rats displayed ataxia and decreased motor activity after 25 to 30 minutes exposure to n-hexane concentrations between 302,720 and 316,800 mg/m^3 (86,000 and 90,000 ppm) (Honma, 1983). Sedation, hypothermia, and ptosis (*i.e.*, drooping of the upper eyelids) occurred in male Sprague-Dawley rats exposed to 7,040, 14,080 and 28,160 mg/m^3 (2,000, 4,000 and 8000 ppm) of n-hexane for eight hours (Raje *et al.*, 1984). In Swiss mice, light anaesthesia occurred after exposure to 56,320 mg/m^3 (16,000 ppm) for five minutes, while deep anaesthesia (with periods of apnoea) occurred during exposure to 112,640 mg/m^3 (32,000 ppm) for the same duration (Swann *et al.*, 1974).

[2] LC50 refers to the concentration required to kill 50% of the test population (*i.e.*, lethal concentration)

Histopathological effects on the lung (as manifested by lamellar inclusions in type II pneumocytes) were observed in Wistar rats exposed to n-hexane (96 to 99% purity) at a concentration of 35,200 mg/m^3 (10,000 ppm) for four or eight hours, or to 24,640 mg/m^3 (7000 ppm) for eight hours (Schnoy *et al.*, 1982; Schmidt *et al.*, 1984). Light and electron microscopy revealed no effects on intrapulmonary nerves.

Sprague-Dawley rats exposed to 17,600 mg/m^3 (5,000 ppm) of 99% pure n-hexane for 24 hours displayed testicular lesions that were characterized by degeneration of primary spermatocytes, and mild exfoliation of spermatids (De Martino *et al.*, 1987). There were no reported deaths or other manifestations of toxicity. Complete recovery occurred within 30 days post-exposure.

Tables 6 and 7 provide a summary of acute human and experimental animal inhalation toxicity studies with n-hexane.

Table 6 Summary of Acute Human Toxicity Studies with n-Hexane

Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
3 to 5 minutes	1,760	No irritation of eyes, nose or throat (purity and isomer composition of hexane not specified)	Nelson *et al.*, 1943
10 minutes	17,600	Vertigo and giddiness	Patty and Yant, 1929
10 minutes	7,040	No vertigo or giddiness	Patty and Yant, 1929
30 to 60 minutes	3,520 to 89,760	Drowsiness	Yamada, 1967
Not reported	4,928 to 5,280	Nausea, headache, eye and throat irritation	Drinker *et al.*, 1943
8 h (time weighted average)	92	Temporary episodes of light-headedness and dizziness	NIOSH, 1981

Table 7 Summary of Acute Inhalation Studies with n-Hexane in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Male Fischer 344 rats	1 h	271,040	LC50	Pryor *et al.*, 1982
Male Fischer 344 rats	Not reported	168, 960	Myoclonic seizures and ataxia	Pryor *et al.*, 1982
Male Fischer 344 rats	10 minutes	84,480	No acute behavioural effects	Pryor *et al.*, 1982
Fischer 344 rats	24 h/d for 5 d/wk for 11	3520	Inhibition of body weight gain, effects on motor activity and behavioural effects; some	Pryor *et al.*, 1982

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
	wks		recovery occurred post-exposure	
Long-Evans rats	4 h	259,354	LC50	Hine and Zuidema, 1970
Sprague-Dawley rats	25 to 30 minutes	302,702 to 316,800	Ataxia and decreased motor activity	Honma, 1983
Male Sprague-Dawley rats	8 h	7,040	Sedation, hypothermia and ptosis	Raje *et al.*, 1984
Swiss mice	5 minutes	56,320	Light anaesthesia	Swann *et al.*, 1974
Swiss mice	5 minutes	112,640	Deep anaesthesia	Swann *et al.*, 1974
Wistar rats	4 or 8 h	35,200	Histopathological effects on lungs	Schnoy *et al.*, 1982 ; Schmidt *et al.*, 1984
Wistar rats	8 h	24,640	Histopathological effects on lungs	Schnoy *et al.*, 1982 ; Schmidt *et al.*, 1984
Sprague-Dawley rats	24 h	17,600	Testicular lesions, recovery occurred post-exposure	De Martino *et al.*, 1987

4.1.3 Subchronic and Chronic Toxicity

It is well established that chronic human exposure to n-hexane results primarily in motor and sensory peripheral neuropathy. The first signs of n-hexane-induced neuropathy are symmetrical paraesthesia and weakness in lower extremities. Headaches and dizziness may precede or coincide with the neuropathy. A sensory impairment to touch, pain, vibration, and temperature develops next, with weakness and atrophy affecting proximal muscles of the extremities. On clinical examination, most patients show reduced body weight and diminished or absent reflexes. There also is marked reduction in conduction velocity of sensory and motor nerves, and electromyographic abnormalities. Axonal lesions of the large myelinated fibres with axonal swelling followed by myelin retraction at the node of Ranvier are often found upon nerve biopsy. There can be slight to moderate reduction in the numbers of fibres, mainly of large myelinated fibres, and myofibrillar atrophy. Recovery is always gradual and slow and signs of residual neuropathy may persist in severe cases for three to four years. Pyramidal tract defects such as residual hyper-reflexia and spasticity, autonomic defects, and central nervous system dysfunction (abnormal evoked potentials) also have been reported in a few severe cases (WHO, 1991). Cranial neuropathies, blurred vision, and abnormal colour vision associated with macular changes also have been reported in subjects with peripheral neuropathy (U.S. EPA, 1990).

A number of epidemiological studies have been conducted that demonstrate the link between occupational exposure to n-hexane and neurological effects, particularly peripheral neuropathy. Peripheral neuropathy has been reported to occur following

exposure to a wide range of n-hexane levels in air, ranging from 30 to 2,500 ppm (106 to 8,800 mg/m^3). In general, workplace exposure to n-hexane at or above 500 ppm (1,760 mg/m^3) for several months may result in peripheral neuropathy in some individuals (ATSDR, 1999). However, determination of a clear exposure-response relationship has been difficult. In most studies, the air concentrations of n-hexane were not measured until after peripheral neuropathy began to occur in workers. Also, in most studies, workers were concurrently exposed to various other chemicals that may have contributed to the observed effects and/or affected the workers response to n-hexane exposure (ATSDR, 1999). Air concentrations for these other chemicals have rarely been documented. Other deficiencies in these studies include lack of accurate exposure estimates, possible exposure by other routes, improper industrial hygiene practices, absence of control populations, failure to report air concentrations altogether, and studies not specifying whether the hexane was a commercial formulation or n-hexane (ATSDR, 1999; WHO, 1991). Because of these limitations, the 500 ppm threshold suggested for peripheral neuropathy cannot be adequately confirmed with any of these studies (U.S. EPA, 1990).

In addition, for studies that reported effects on peripheral nerve electrophysiology, measures vary considerably depending on a number of parameters other than n-hexane exposure such as the type of technique used, the ambient temperature at which measurements were taken, the segment of the nerve studied, and the age of the individual (WHO, 1991). Thus, the interpretation of studies that rely on peripheral nerve electrophysiology data is difficult in the absence of information on these factors. There is also uncertainty regarding intra-individual differences in susceptibility to n-hexane peripheral neuropathy. For example, Chang *et al.* (1993) showed that some n-hexane exposed individuals develop peripheral neuropathy within months, whereas others remain symptom-free despite years of employment at the same occupation.

Yamada (1967) reported polyneuropathy, with subsequent development of muscular atrophy and paraesthesia in the distal extremities in 17 workers exposed to n-hexane concentrations between 500 ppm (1,760 mg/m^3) and 1,000 ppm (3,520 mg/m^3) in a pharmaceutical plant.

A study of 93 sandal manufacturing workers with peripheral neuropathy was conducted by Yamamura (1969). Urinalysis, haematology and serum chemistry, electromyography, and nerve conduction tests were performed on 42 to 44 of the 93 cases. The case group consisted of 21 males and 72 females with an average age of 40.6 years. These subjects were divided into three groups: Group I, sensory neuropathy only (53 cases); Group II, sensorimotor neuropathy (32 cases); and Group III, sensorimotor neuropathy with muscle atrophy (eight cases). The authors stated that n-hexane concentrations in the subjects work areas ranged from 500 to 2,500 ppm (1,760 to 8,800 mg/m^3). Durations of exposure were not specifically mentioned in the study. The most common initial symptom was numbness in the distal portions of the extremities (88%); the second most common was muscle weakness (14%). Major clinical findings were numbness (100%); muscle weakness (43%); hypoactive reflexes (38.7%); and coldness, reddishness, or roughness of the skin (59.2%). Central nervous system effects were not observed in any

subject. All the cases in Group III showed a continuing increase in the severity of peripheral neuropathy for one to four months after exposure ceased. A follow-up study of 36 patients showed complete or near-complete recovery between 3 and 18 months post-exposure. Electromyography revealed the appearance of fibrillation voltages (indicating denervation) and positive sharp waves in 15.3 and 19.9% of examined muscles in groups II and III, respectively. Reduction of motor nerve conduction velocity in median and ulnar nerves was observed in 22 and 16 cases, respectively. Tibial motor nerve conduction velocity was reduced in 31 cases, and peroneal nerve motor nerve conduction velocity was reduced in 21 cases. The authors stated that reduction in motor nerve conduction velocity was greatest in Group III, followed by Group II and then Group I. Atrophy of muscle fibres was noted in the tibial muscle of three cases. Biopsies of peripheral nerves in six cases revealed demyelination and infiltration of leukocytes in perivascular areas. Axonal degeneration also was present.

Herskowitz *et al.* (1971) conducted a case series study of workers in a furniture factory in the Bronx, New York. Three women who worked as cabinet finishers, wiping glue off furniture with rags soaked in a solvent that contained n-hexane, were evaluated. The women worked in a poorly ventilated room where an open drum of solvent was used. Air concentrations of n-hexane averaged 650 ppm (2,288 mg/m^3), although peaks of up to 1,300 ppm (4,576 mg/m^3) were reported. Neurological signs of both motor and sensory impairment were observed in all three women with an onset two to four months after beginning employment. The symptoms and clinical findings were similar in all three women. Initial symptoms included a burning sensation in the face, numbness of the distal extremities, progressive distal symmetrical weakness in all extremities, frequent headaches, and abdominal cramps. Subsequent muscle testing revealed a moderate distal symmetrical weakness and a bilateral foot-drop gait. There was also a moderate decrease of pin and touch perception and mild impairment of vibration and position sense in the lower extremities. There was no indication of central nervous system toxicity. Blood chemistry results were within normal limits. Electromyography revealed fibrillation potentials in the small muscles of the hands and feet. Nerve conduction velocities were reduced in the left ulnar, the right median nerve, and the left peroneal nerve. Muscle biopsy results showed evidence of denervation. Electron microscopy of nerve branches within the muscle showed an increased number of neurofilaments with abnormal membranous structures, and clumping and degeneration of mitochondria with dense bodies.

Sanagi *et al.* (1980) conducted an epidemiology study on two age-matched groups consisting of 14 control workers and 14 exposed workers employed in a factory producing tungsten carbide alloys. The groups were matched with respect to age, height, weight, alcohol consumption and smoking habits. Exposure was estimated using 22 personal samples taken from the breathing zones over two years and reported as an eight-hour TWA exposure concentration. Airborne n-hexane was reported to be 58 ± 41 ppm (204 ± 144 mg/m^3) (duration-adjusted concentration was 73 mg/m^3). Acetone also was measured in the workplace air at 39 ± 30 ppm. No other solvent vapours were detected. The exposure duration of the groups ranged from 1 to 12 years with an average of 6.2 years. No neurological abnormalities were noted in the two groups. However, neurophysiological tests showed that the mean motor nerve conduction velocities of the

exposed group were significantly decreased relative to controls. Also, the residual latency of motor nerve conduction of the posterior tibial nerve was significantly slowed in the exposed group versus the controls. In a questionnaire, the prevalence of headaches, dysesthesia of limbs, and muscle weakness was higher in the exposed group compared to the controls. Paraesthesia of the extremities was observed in three exposed workers and one worker in the control group. A general trend of diminished strength reflexes was found in the biceps and knees of exposed workers; however, the difference was not statistically significant. The U.S. EPA (1990) identified a LOAEL of 73 mg/m^3 from this study.

It is not clear if the acetone co-exposure in the Sanagi *et al.* (1980) study contributed to the observed effects. Cardona *et al.* (1996) showed that workplace acetone concentrations had a statistical correlation with the ratio of urinary n-hexane metabolites to n-hexane air concentration, although it did not correlate with measured urinary metabolites. No animal studies are available describing the effects of inhalation co-exposure to acetone and n-hexane, although there are studies that report interactions between acetone and 2,5-hexanedione by the oral route. For example, oral administration of acetone potentiated the neurotoxicity of 2,5-hexanedione in rats (Ladefoged *et al.*, 1989; 1994). Thus, it is possible that the effects of n-hexane in this study were influenced by co-exposure to acetone.

Wang *et al.* (1986) conducted a cross-sectional study of press-proofing workers in Taipei, Taiwan. A total of 59 workers from 16 press-proofing factories were examined. Workers were exposed to n-hexane-containing solvents during a cleaning process. The authors defined polyneuropathy as the presence of objective signs (*e.g.*, the inability to walk-on-heels and/or walk-on-toes) as well as at least one abnormally slow conduction velocity in both the upper and the lower extremities, or two abnormally slow nerve conduction velocities in the lower extremities. Of the 59 workers examined, 15 (25%) were diagnosed with neuropathy. Among these individuals, the duration of employment ranged from 7 months to 5 years. There were three separate factories where workers had polyneuropathy. Eight workers were from a factory that had closed, so no air measurements were possible. Two workers were from a factory where the measured n-hexane concentration was 22 ppm (77.4 mg/m^3) (this was considered an underestimate since the door was open and ventilation fans were running at time of sampling, while the usual workplace condition was a closed-off work area). Six workers were from a factory where the measured n-hexane concentration was 190 ppm (669 mg/m^3). In all cases, air samples were collected for a single random one-hour period only. As such, it is not known how representative they are of actual worker exposures. Most workers were exposed for more than eight hours a day as a result of overtime, and there were 13 who regularly slept at the factory. Twelve of these thirteen who slept in the factory had polyneuropathy compared to only 3 of 46 who slept elsewhere. No significant correlation between neuropathy and length of employment or age was found. It was reported that other chemicals known to cause neurotoxicity were not present in significant amounts. All cases of neuropathy occurred in factories using solvents containing >50% n-hexane. Sural nerve biopsies of three diagnosed individuals showed axonal degeneration and secondary changes in the myelin sheath. Decreased motor nerve conduction velocities also were observed in a number of workers.

In a study of 56 workers at an offset printing factory, clinical peripheral neuropathy was noted in 20 of 56 (36%) workers, while another 26 (46%) presented with subclinical neuropathy (Chang *et al.*, 1993). The workers spent 12 hours per day for six days per week at the factory. The mean duration of employment was 2.6 years, with a range of one month to 30 years. Reduced sensory action potentials, as well as reduced motor action potentials, decreased motor nerve conduction velocity, and increased distal latency were observed in most workers. In a severe case, giant axonal swellings with accumulation of 10 nm neurofilaments, myelin sheath attenuation, and widening of nodal gaps were noted upon sural nerve biopsy. Optic neuropathy and CNS impairment were not significant in the workers. Personal air samples of workers contained 80 to 210 ppm (282 to 739 mg/m^3) hexane (mean = 132 ppm; 465 mg/m^3), but also contained 20 to 680 ppm isopropanol (mean = 235 ppm), and 20 to 84 ppm (mean = 50 ppm) toluene. Plant n-hexane concentrations ranged from 30 to 110 ppm (106 to 387 mg/m^3) (mean = 63 ppm; 222 mg/m^3).

Yokoyama *et al.* (1990) evaluated three male workers, 23 to 27 years old, who developed peripheral neuropathy after being exposed to n-hexane in the workplace for roughly six months. A single measurement of atmospheric n-hexane was 195 ppm (686 mg/m^3). Conduction velocities in the sural nerve of these workers were reduced relative to a group of control subjects (11 males aged 23 to 40).

Mutti *et al.* (1982a,b,c) reported a cross-sectional study using age-matched controls of workers in a shoe factory exposed to n-hexane. The exposed group was composed of 24 males and 71 females with a mean age of 30.9 years and mean employment time of 9.1 years. The control group consisted of 12 males and 40 females with a mean age of 29.6 years and mean employment time of 10.2 years. The exposed group was subdivided into a mild and high-exposure group on the basis of time-weighted average breathing-zone air samples (108 samples were taken over a two-year period). Mean breathing-zone n-hexane air concentrations were 69 ppm (243 mg/m^3) in the mild-exposure group and 134 ppm (472 mg/m^3) in the high-exposure group. Cyclohexane, methyl ethyl ketone, and ethyl acetate also were detected. The presence of these other solvents may have affected responses to n-hexane as methyl ethyl ketone, in particular, is known to potentiate n-hexane neurotoxicity. Sleepiness and dizziness were reported to be more frequent during the workday in the exposed groups than in the control group. The exposed groups also displayed such effects as weakness, paraesthesia, and hypoesthesia. Motor action potential amplitude in three examined nerves was significantly decreased in the exposed groups relative to controls. Motor nerve conduction velocity was significantly decreased in median and peroneal nerves, but not in the ulnar nerve of the exposed groups. In the median nerve, motor nerve conduction velocity was significantly decreased in the high-exposure group compared to the mild-exposure group. A case-control study also was conducted on workers from this shoe factory (Mutti *et al.*, 1982b). Fifteen women from this factory (mean age = 26.6 years; mean exposure time = 4.5 years) were compared to a control group of 15 healthy age-matched women from other shoe factories who had not been exposed to neurotoxic solvents. The mean time-weighted average n-hexane air concentration was 195 ppm (686 mg/m^3) for 36 samples taken over a three-year period in the factory. Methyl ethyl ketone also was present at

60 ppm. The authors noted that these concentrations had been substantially reduced three months earlier when industrial hygiene practices had improved; this resulted in n-hexane air concentrations being at trace levels at the time nerve conduction measurements were taken. All nerve conduction velocities (motor and sensory) were significantly slowed in exposed workers compared to controls. Also, sensory nerve action potential peak latency was significantly higher in the median and ulnar nerves of the exposed workers. Nerve conduction velocities were not age-dependent in the exposed group but were in the control group.

In a follow-up study, 90 shoe manufacturing workers (27 men and 63 women) diagnosed in the past with n-hexane polyneuropathy were studied at least 1 year after cessation of n-hexane exposure (Valentino, 1996). Urinary 2,5-hexanedione levels were analyzed in the urine in more than half of the workers to confirm that n-hexane exposure had ceased. Group A consisted of 63 subjects with a mean exposure duration of 8.9 years. Group B consisted of 27 subjects with a mean exposure duration of 9.2 years. At the time of the follow-up, the mean age of subjects in group A was 44.4 years and was 52.9 years in Group B. A control group of 18 men and 20 women with a mean age of 38.8 years was used (Group C). Groups A and B were not significantly different from each other with respect to symptoms related to polyneuropathy. Paraesthesia and weakness in legs or arms were reported by 22% and 28% of Group A subjects, respectively, and by 28% and 35% of Group B subjects, respectively. The percentage of subjects with abnormal leg tendon reflexes, leg cutaneous sensitivity or vibration sensation, and arm vibration sensation was statistically higher in subjects who had ceased n-hexane exposure for less than ten years. No differences were found between Group A and Group B for arm deep tendon reflexes and arm cutaneous sensation, or in electrophysiological parameters. Motor nerve conduction velocities and distal latencies in Groups A and B had improved from the time of diagnosis and were similar to the control group. However, sensory nerve conduction velocities and distal latencies, while improved from the time of diagnosis, remained statistically different from controls. This study suggests that peripheral neuropathy effects of n-hexane can persist for more than one year after exposure has ceased.

A group of 15 industrial workers exposed to n-hexane in vegetable oil extracting and adhesive bandage manufacturing plants were examined for signs of neurotoxicity and ophthalmological changes (Raitta *et al.*, 1978; Seppalainen *et al.*, 1979). The workers (11 males and four females) had been exposed to n-hexane for a period of five to 21 years. Ten healthy unexposed workers served as controls. Exposures to n-hexane were reported to be variable and ranged as high as 3,000 ppm (10,560 mg/m^3) on occasion, but were typically below 500 ppm (1,760 mg/m^3). The type of work performed resulted in high short-term exposures that lasted up to two hours at a time. Visual evoked potentials (VEPs) were generally reduced among the exposed subjects and latencies tended to be increased (Seppalainen *et al.*, 1979). Visual acuity, visual fields, intraocular pressure, and biomicroscopical findings were all normal and similar to the control group. Macular changes were noted in 11 exposed workers and impaired color discrimination was found in 12 of the 15 exposed workers, mainly in the blue-yellow spectrum (Raitta *et al.*, 1978).

Issever *et al.* (2002) studied colour discrimination in 26 workers diagnosed as having polyneuropathy following n-hexane exposure. The FM-100 Hue test was used to determine colour discrimination in the workers. Results were compared with a control group of 50 people who had not been exposed to n-hexane. The mean total error score for the exposed group was 168.3 for the right eye and 181.5 for the left eye. The mean total error scores for the control group for the right and left eyes were 36.0 and 35.6, respectively. Differences between total and partial error scores for exposed versus control groups were statistically significant ($p < 0.001$). These results suggest a relationship between n-hexane exposure and development of defects in colour vision. Exposure to 2,5-hexanedione, a major n-hexane metabolite, has been shown also to cause loss of photoreceptor cells, particularly when combined with light energy (Backstrom *et al.*, 1998).

The current review came across one report of immunological effects in humans after exposure to n-hexane. Karakaya *et al.* (1996) reported a reduction in immunoglobulin levels in a group of 35 male workers, relative to a control group of 23 age-matched, unexposed workers. The reductions in immunoglobulin levels correlated with 2,5-hexanedione levels in urine but not with workplace n-hexane air concentrations, which ranged from 23 to 215 ppm (81 to 757 mg/m^3). The reductions also remained well within the normal ranges for immunoglobulins in blood, so the toxicological significance of these findings is doubtful (Jackson *et al.*, 1997). Cell counts of lymphocytes, neutrophils, monocytes, eosinophils were unaffected by n-hexane exposure.

Two case reports (Pezzoli *et al.*, 1989; 1995) suggest an association between n-hexane and Parkinson's syndrome, but this has not been confirmed in any other studies identified to date.

Table 8 provides a summary of the subchronic and chronic human studies with n-hexane or commercial hexane mixtures.

In subchronic and chronic experimental animal studies, symptoms of peripheral neuropathy are commonly reported. Muscle atrophy is a common feature following inhalation exposure to n-hexane in experimental animals, as it is a secondary effect of neuropathy that results in muscle denervation (ATSDR, 1999). Respiratory effects also have been reported to occur in animal studies, but only at concentrations that are substantially higher than those that cause neurotoxicity. Thus, respiratory effects do not appear to be a sensitive indicator of n-hexane toxicity in animals (ATSDR, 1999). Effects on body weight are common during subchronic and chronic exposure of rats to n-hexane and tend to precede the development of neurotoxicity (ATSDR, 1999). There is a correlation between body weight effects and neurotoxicity in animal studies with less severe body weight effects observed in species that are less susceptible to n-hexane-induced neurotoxicity (ATSDR, 1999).

Table 8 Summary of Sub-Chronic and Chronic Human Toxicity Studies with n-Hexane

Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Not provided	1,760 and 3,520	Polyneuropathy, development of muscular atrophy and paraesthesia in distal extremities	Yamada, 1967
2 to 4 months (actual exposure period not provided)	2,288 to 4,576	Motor and sensory impairment	Herskowitz *et al.*, 1971
1 to 12 years (average 6.2 years)	73 (duration-adjusted)	LOAEL: neurophysiological effects (acetone also detected and measured)	Sanagi *et al.*, 1980
9.1 years (mean)	243 to 472	Sleepiness, dizziness, weakness, paraesthesia and hypoesthesia. Motor effects also reported. Other solvents also were detected.	Mutti *et al.*, 1982 a,b,c
4.5 years (mean)	686	Motor and sensory nervous system effects	Mutti *et al.*, 1982b

A large number of studies have investigated both commercial hexane mixtures and high purity n-hexane for their toxicity in experimental animals. The tested commercial hexane mixtures resulted in considerably lower toxicity than studies that tested high purity n-hexane alone.

Body weight gain was reduced in Sprague-Dawley rats exposed for up to six months, for 22 hours per day, to an n-hexane (95% pure) concentration of 1,760 mg/m^3 (500 ppm) (API, 1983a,b).

De Martino *et al.* (1987) reported that motor nerve conduction velocity was significantly decreased by one week into treatment (11% less than controls) in male Sprague-Dawley rats exposed to 17,600 mg/m^3 n-hexane for 16 hours a day, 6 days a week for 6 weeks. Mean reductions ranged from 20 to 34% from the second to the fourth week. By four to six weeks of exposure, clinical signs of neurotoxicity became evident in most test animals.

Miyagaki (1967) continuously exposed groups of SM-A male mice to 0, 100, 250, 500, 1,000, or 2,000 ppm (0, 353, 881, 1,762, 3,525, or 7,050 mg/m^3) commercial grade hexane (which contained 65 to 70% n-hexane), for six days per week for one year. The remaining hydrocarbons in the mixture were described as other hexane isomers. Duration-adjusted concentrations were reported by U.S. EPA (1990) as 0, 302, 755, 1,510, 3,020, or 6,040 mg/m^3). Electromyographic analysis showed a dose-related increased complexity of neuromuscular unit voltages in zero of six controls, one of six animals in the 100 ppm group, three of six animals in the 250 ppm group, five of six

animals in the 500 ppm group, three of three animals in the 1,000 ppm group, and four of four animals examined in the 2,000 ppm group. Electromyography showed a similar dose-related increase in the incidence and severity of reduced interference voltages from muscles in animals exposed to 250 ppm and higher, but not in the controls or the 100 ppm group. A dose-related increase in abnormalities of strength-duration curves also was noted. Slight fibrillation was detected in the electromyograms of no mice in the 100 ppm exposure group, two of six mice in the 250 ppm exposure group and no mice in the 500 ppm group. Severe fibrillation was noted in three of three animals examined in the 1,000 ppm group and in four of four in the 2,000 ppm group. Abnormal posture and muscle atrophy also were noted, in a dose-related manner, in animals exposed to concentrations of n-hexane at 250 ppm and higher (however, the highest exposure group showed an unexplained resumption of normal posture in three of four animals examined). This study indicates a neurotoxicity threshold between 100 and 250 ppm in mice, as neurotoxic effects were observed in mice exposed to greater than 250 ppm. A NOAEL of 100 ppm (352 mg/m^3) was identified from this study. When this NOAEL was adjusted for 70% n-hexane in the test mixture, the n-hexane NOAEL becomes 246 mg/m^3. The fact that only findings for three to six of the 10 animals per test group were presented limits the significance of this study.

In a study by Bio/Dynamics (1978), Sprague-Dawley rats (12 per sex per dose) were administered n-hexane vapour (purity not stated) at concentrations of 0, 6, 26, or 129 ppm (0, 21, 92, or 455 mg/m^3) for 6 hours per day, 5 days per week, for 26 weeks (duration-adjusted concentrations were 0, 3.8, 16.4, or 81 mg/m^3) and at 0, 5, 27, or 126 ppm (0, 18, 95, or 444 mg/m^3) for 21 hours per day, 7 days per week, for 26 weeks (duration-adjusted concentrations were 0, 15.4, 83, or 389 mg/m^3). No rats exhibited the characteristic pathological signs of nervous system degeneration produced by n-hexane. A NOAEL of 389 mg/m^3 was identified from this study. However, it should be recognized that these two studies suffered from a number of limitations, which question the validity of this NOAEL, including lack of a proper key to associate specific animals to their dose groups, the small numbers of animals tested, and the fact that examinations were limited to physical observation, body weight, hematological parameters, clinical chemistry, and necropsy upon spontaneous death.

Daughtrey *et al.* (1999) investigated the carcinogenic and chronic toxicity potential of commercial hexane solvent in F-344 rats and B6C3F1 mice exposed by inhalation for 6 hours per day, 5 days per week for 2 years. The findings of this study related to carcinogenicity are described in Section 4.1.6. Tested hexane vapour concentrations were 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3). There were no significant differences observed in survivorship between control and hexane-exposed groups, and there were only minor clinical observations in the exposed groups. Statistically significant decreases in body weight gain were observed in rats of both sexes in the mid- and high-exposure groups and in the high-exposure female mice. The only noteworthy histopathological finding reported in rats was epithelial cell hyperplasia in the nasoturbinates and larynx of the exposed groups. This response was considered due to upper respiratory tract irritation. No neuropathological effects were reported in this study.

Schaumburg and Spencer (1976) exposed Sprague-Dawley rats (sex not specified) continuously to an air concentration of 400 to 600 ppm (1,408 to 2,112 mg/m^3) n-hexane for up to 62 days. The rats developed an unsteady, waddling gait between days 45 to 69 of exposure. Further exposure resulted in a progressive, symmetrical, distal hind limb weakness with foot-drop. The most severely affected animals also developed distal weakness of the upper extremities. Pathological changes, including giant axonal swellings and nerve fibre degeneration, were detected in the peripheral and central nervous systems of four animals exposed for 49 days. Electron microscopic examination showed that the swollen axonal regions contained densely packed masses of 10 nm neurofilaments. The nerve fibre most vulnerable to n-hexane exposure in this study were the branches of the tibial nerve serving the calf muscles, followed by the plantar nerve branches, and then sensory plantar nerve branches innervating the digits.

New Zealand rabbits exposed to 3,000 ppm (10,560 mg/m^3) n-hexane for 8 hours a day, 5 days a week for 24 weeks showed no signs of peripheral neurotoxicity (Lungarella *et al.*, 1984). However, there were signs of respiratory tract irritation, increased nasal discharge and breathing difficulties (gasping, lung rales, mouth breathing) throughout the study. Upon histological examination, gross lung changes observed in the rabbits included collapsed dark red areas, hyperemia, and the accumulation of mucous material. The trachea and the major bronchi showed areas of epithelial desquamation, atrophy, flattening of the mucosa, and foci of goblet cell metaplasia. The distal regions of terminal bronchioles and proximal portions of the alveolar ducts contained air space enlargements (consistent with centrilobular emphysema), scattered foci of pulmonary fibrosis, and papillary tumours of the bronchiolar epithelial cells. None of these lung changes were observed in controls. Two of 12 rabbits died during the study, possibly due to respiratory failure. The authors also studied the reversibility of these lung effects. A group of five rabbits were kept for 120 days after exposure ceased and were examined. There were no histopathological changes visible in the mucosa of the trachea and the major bronchi except for small, scattered foci of goblet cell metaplasia. However, irregular foci of cellular proliferation and papillary tumours in terminal bronchiolar and alveolar ducts persisted.

NTP (1991) conducted a 13-week inhalation toxicity study of n-hexane with B6C3F1 mice (this study was also reported in Dunnick *et al.*, 1989). Mice of each sex (10 per sex per dose) were exposed to 0, 500, 1,000, 4,000, or 10,000 ppm (0, 1,760, 3,520, 14,080 and 35,200 mg/m^3), for 6 hours per day, 5 days per week, or to 1,000 ppm for 22 hours per day, for 5 days per week (this was termed "1000c"). All mice survived the experiment. Mean body weights of mice in the 1000c and 10,000 ppm group were 10% and 17% lower than that of the controls for males. Body weight changes were minimal for females. Hematological analyses showed that segmented neutrophils were significantly increased in male mice exposed to 10,000 ppm. The only neurobehavioral effect noted was decreased locomotor activity in female mice in the 1000c and 10,000 ppm groups. A few paranodal swellings in the teased fibers of the tibial nerve were observed in three of four males and three of four females exposed to 10,000 ppm, and in three of four males and three of four females in the 1000c group. These effects

were not seen in controls. The lesions were noted as not being severe and neither segmental demyelination nor distal axonal degeneration was observed. Lesions of the respiratory tract and nasal turbinates were seen in all groups of exposed mice except males in the 500 and 4,000 ppm groups. At the 10,000 ppm exposure level, nasal lesions included inflammatory, erosive, and regenerative lesions of the olfactory and respiratory epithelium; luminal exudation and metaplastic lesions of the olfactory epithelium; and fibrosis of the submucosa. Lymphoid hyperplasia of the mandibular lymph nodes and neutrophilic hyperplasia of the bone marrow were also seen at this concentration. Sneezing was also reported at the 10,000 ppm concentration, which began at week four and continued until the end of the study. At lower concentrations, these lesions were not present in all mice and were limited to minimal regeneration, or metaplasia of the olfactory epithelium. No respiratory effects were noted in the 500 ppm group. It was concluded that exposure of mice to n-hexane at concentrations up to 10,000 ppm resulted in only minimal toxicity, and minimal or no adverse effects were seen at n-hexane concentrations of 1,000 ppm or lower. A LOAEL of 1,000 ppm (3,520 mg/m^3) and a NOAEL of 500 ppm (1,760 mg/m^3) were identified from this study.

The U.S. EPA (1990) and OEHHA (2003) noted that interpretation of the results of this study is limited by the fact that neuropathological examinations were conducted only in the 1000c, the 10,000 ppm group and the controls. These examinations were not performed in the groups that represent the LOAEL or NOAEL.

IRDC (1981) exposed groups of male Charles River rats (14 per group) to n-hexane plus mixed hexane isomers for 22 hours per day, 7 days a week for approximately six months. The test concentrations were 0 and 126 ppm n-hexane (444 mg/m^3; duration-adjusted = 407 mg/m^3), 125 ppm n-hexane + 125 ppm mixed hexanes, 125 ppm n-hexane + 375 ppm mixed hexanes, 125 ppm n-hexane + 1,375 ppm mixed hexanes, and 502 ppm n-hexane (1,769 mg/m^3; duration-adjusted = 1,622 mg/m^3). No deaths were reported. Body weight declines were observed in both groups exposed to n-hexane, but not in the n-hexane + mixed hexanes groups. Neurotoxicity of the peripheral nervous system was observed in rats exposed to 502 ppm n-hexane. The most significant observations were abnormal gait, axonal degeneration, and myelin vacuolization. No central nervous system effects were noted. The authors concluded that neurotoxicity appeared to be a specific response of n-hexane exposure, as no other treatment groups developed neuropathological effects. Mild necrotic liver changes were observed in some rats, although this effect was not dose related. There was also no dose-related increase in severity or incidence of adverse effects in the nasal turbinates. Changes in average absolute and relative organ weights were noted for the liver and kidney in rats exposed to 125 ppm n-hexane + 1,375 ppm mixed hexanes, and in the liver of rats exposed to 502 ppm n-hexane only. This study identified a NOAEL of 125 ppm (440 mg/m^3).

A study that compared continuous n-hexane exposure to intermittent exposure found that male Wistar rats exposed to 500 or 700 ppm (1,760 or 2,464 mg/m^3) of n-hexane for 22 hours per day for nine weeks showed signs of narcosis and limb weakness (Altenkirch *et al.*, 1982). The limb weakness began in the hind limbs, and eventually lead to paralysis and quadriplegia. Complete hind limb paralysis was exhibited in the ninth week by all animals exposed to 500 ppm. Animals exposed to 700 ppm n-hexane exhibited hind limb

paralysis by the fourth week of exposure. Light microscopy examination of peripheral nerves revealed patterns of scattered multifocal giant axonal swellings localized primarily in the branches of the tibial nerve supplying the calf muscles, and also in other portions of the ischiatic nerve. Breakdown of axons and myelin degradation were visible distal to axonal swellings. Axonal swellings were also observed in the gracile tract of the spinal cord at cervical levels. In contrast to these results, daily exposure at 700 ppm for up to 8 hours per day, for up to 40 weeks did not result in clinical signs of neurotoxicity (Altenkirch *et al.*, 1982).

Cavender *et al.* (1984) conducted a 13-week inhalation study in Fischer rats (5 per sex per dose). Test concentrations were 0, 3,000, 6,500, or 10,000 ppm of >99.5% pure n-hexane (0, 10,560, 22,880, or 35,200 mg/m^3) and were administered 6 hours per day, 5 days per week. Duration-adjusted concentrations were 0, 1,888, 4,091, or 6,294 mg/m^3. No significant differences were observed in female body weights, clinical observations, food consumption, ophthalmologic examination, neurological function, or hematological or serum chemistry parameters for either sex. Male brain weights were significantly lower in the 10,000 and 3,000 ppm groups males relative to controls, but not in males of 6,500 ppm group. The mean body weight gain of male rats in the 10,000 ppm group was significantly decreased relative to controls by 4 weeks exposure and throughout the duration of the study. Isolated and greatly enlarged axons were noted in the medulla of one male in the 10,000 ppm group. No other histopathologic lesions were present in the brain that could be attributed to n-hexane exposure. Neuropathological studies on peripheral nerves revealed signs of axonopathy in the tibial nerve in four of five males from the 10,000 ppm and one of five males from the 6,500 ppm group. All lesions were at an early stage of development and consisted of paranodal axonal swelling in teased fibres from the nerve, with the most severe swellings noted in the smaller branches of the sciatic nerve. No evidence of demyelination or axonal degeneration was observed. No consistent changes were observed in any male or female rats from the 3,000 ppm group. Thus, this study identified a NOAEL of 3,000 ppm (10,560 mg/m^3).

Howd *et al.* (1983) studied the effect of age on the rate of development and severity of effects of n-hexane exposure in weanling (21 days old) and young adult (80 days old) male Fischer 344 rats exposed to 0 or 1,000 ppm (3,520 mg/m^3) for 24 hours per day, 6 days per week for 11 weeks. In general, adverse effects had an earlier onset and were more severe in young adults than in weanlings. Weanlings also recovered completely by four weeks post-exposure. However, for the young adult rats, two of ten had died by the end of the study, and all had flaccid paralysis of the hind limbs. Only slight recovery occurred by four weeks post-exposure. Within two weeks of exposure, decreases in grip strength were apparent in rats of both ages. Hind limb grip strength was decreased more than forelimb grip strength, and the young adults were more severely affected than weanlings. In both groups, motor nerve action potential latency began to increase by seven weeks while the amplitude decreased. By the end of the study, action potential amplitude had decreased so much that action potentials could not be detected in many of the exposed rats during the recovery period. There were no differences between weanling and young adult rats in their brainstem auditory-evoked responses when measured after four weeks. The latency of the first component of the brainstem auditory-evoked responses increased in both exposed groups relative to controls. This effect was

significant from week seven through nine in weanlings and from week seven to the end of the study in young adults. Body weight of rats was also adversely affected. By the end of the study, the body weight of young adults was 54% below that of controls and that of weanlings was 33% below control. The young adults failed to gain any weight over the exposure duration. The authors suggested that the relative resistance of the weanling rats to n-hexane neuropathy might be due to shorter, smaller-diameter axons, or to a higher rate of growth and repair in their peripheral nerves than adults.

Rebert and Sorenson (1983) exposed male Fischer 344 rats to 0, 500, 1,000 or 1,500 ppm (0, 1,760, 3,520, or 5,280 mg/m^3) n-hexane for 24 hours per day, 5 days per week, for 11 weeks. There was a six-week recovery period in which surviving rats were observed. Body weights of in the 1,500 ppm group were 11% below those of control rats by two weeks. Forelimb and hind limb grip strengths were significantly decreased at all tested concentrations by four weeks. Recovery was found to be concentration-dependent, and was fastest in rats in the 500 ppm group and slowest in the 1,500 ppm group. Ventral caudal nerve action potential latency was found to be unaffected at 500 ppm, but increased significantly in the 1,500 ppm group by three weeks. This continued to increase during the recovery period in the 1,000 and 1,500 ppm groups. Somatosensory-evoked responses (recorded in the brain) were unaffected in the 500 ppm group, but both latency and amplitude were affected in the 1,000 and 1,500 ppm groups. There was little recovery from this effect. In contrast, effects on the brainstem auditory-evoked response and cortical auditory-evoked response recovered well post-exposure. Although there was reduced forelimb and hind limb grip strength at 500 ppm (1,760 mg/m^3), this concentration was considered to be a NOAEL as rats recovered quickly from this effect at this exposure level.

Weanling male Fischer 344 rats exposed for 14 hour per day, 7 days per week, for 14 weeks to 7,040 mg/m^3 (2,000 ppm) of 95% pure n-hexane showed a variety of behavioural and neurophysiological effects, including reduced motor activity, startle response, pole-climbing ability, avoidance response, and grip strength, by week two of treatment (Pryor *et al.*, 1983). In addition, tail nerve latency was prolonged from week eight, visual evoked cortical response was increased at six weeks, and there was a reduced amplitude of the fifth brainstem auditory-evoked response (BAER) from week 10. There was no recovery of the tail nerve latency or the BAER component. The visual-evoked cortical response had fully recovered by one week post-exposure.

Takeuchi *et al.* (1980) exposed groups of male Wistar rats to 3,000 ppm (10,560 mg/m^3) of n-hexane for 12 hours a day for 16 weeks. An unsteady and waddling gait was observed in one rat after 10 weeks of exposure. After 12 weeks, four rats had an unsteady, waddling gait and two rats displayed foot-drop. These two rats died one and three days before the end of the exposure period. All surviving rats showed an unsteady waddling gait and two had foot-drop. Motor nerve and mixed nerve conduction velocities were significantly decreased by four weeks and became progressively slower throughout the study. Distal latencies were increased. Histological examination showed that rats had paranodal swelling in myelinated nerves and accumulation of neurofilaments in axons. Many denervated neuromuscular junctions were also observed. Electron microscopy of the gastrocnemius and soleus muscles revealed denervation, irregular

fibers, disordered myofilaments, and numerous invaginations of the plasma membrane. Reduction in body weight (relative to controls) was significant by four weeks, and final body weight was 33% less than controls by study termination. Following daily inhalation of 3,696 mg/m^3 (1,050 ppm) of 99% pure n-hexane for 12 hours a day for 16 weeks, tail nerve conduction velocity in male Wistar rats was reduced, but there were no clear clinical signs of neurotoxicity (Takeuchi *et al.*, 1981). Another study with rats using n-hexane concentrations of 722 or 1,725 mg/m^3 (205 or 490 ppm) exposed for 24 weeks reported similar findings (Ono *et al.*, 1982). Axonal swelling and demyelination were observed in the tail nerves after 24 weeks of exposure to 722 mg/m^3. There were no significant effects on tail nerve conduction time in rats exposed to 373 mg/m^3 (106 ppm) for 12 hour a day, 7 days per week, for 24 weeks (Takeuchi *et al.*, 1983).

Frontali *et al.* (1981) exposed male Sprague Dawley male rats to 0, 500, 1,500 or 5,000 ppm of 99% purity n-hexane (0, 1,762, 5,286, or 17,624 mg/m^3 (the duration-adjusted concentrations = 0, 472, 1,416, or 4,721 mg/m^3), for 9 hours per day, 5 days per week, for 14 to 30 weeks, or to 2,500 ppm (8,812 mg/m^3; duration-adjusted concentration = 3,147 mg/m^3) for 10 hours per day, 6 days per week for 14 to 30 weeks. A significant decrease in weight gain was observed in rats in the 5,000 ppm and 500 ppm groups, but not the 1,500 ppm group. No clinical signs of neurotoxicity were noted in any of the exposed groups. Histopathological examination showed no effect on tibial nerve branches at 500 and 1,500 ppm for any duration up to 30 weeks. Exposure to 5,000 ppm for seven weeks caused no effects. Paranodal and internodal swellings of axons were observed in rats treated intermittently with 2,500 ppm (after 30 weeks) and 5,000 ppm n-hexane (after 14 weeks). This study identified a duration-adjusted NOAEL of 1,416 mg/m^3 for peripheral neuropathy effects.

Huang *et al.* (1989) exposed male Wistar rats to >995 pure n-hexane at 0, 500, 1,200, or 3,000 ppm (0, 1,762, 4,230, 10,574 mg/m^3), for 12 hours a day, seven days per week for 16 weeks (duration-adjusted concentrations = 0, 881, 2,115, or 5,287 mg/m^3). A dose-dependent peripheral neurotoxicity was observed. Body weight gain and motor nerve conduction velocity in exposed groups showed a progressive concentration-dependent decrease relative to controls. Body weight was significantly reduced in the two highest exposure groups, but only slightly in the 500 ppm group. Motor nerve conduction velocity was significantly reduced at 1,200 ppm and 3,000 ppm. No significant decrease was seen at 500 ppm. From week 12, a marked decrease in grip strength and "slowness of action" were observed in the 3,000 ppm and 1,200 ppm groups. However, by the end of exposure, no rats displayed quadriplegia or hind limb paralysis. Histopathologic examination revealed degeneration of peripheral nerves characterized by paranodal swellings and demyelination and remyelination in the myelinated nerve fibres in the two highest exposure groups. No such abnormalities were observed in the 500 ppm group and the control rats. This study identified a NOAEL (HEC) of 881 mg/m^3.

Duffy *et al.* (1991) exposed rats and mice to 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3) commercial hexane for 6 hours per day, 5 days per week for 13 weeks. In both species, the only adverse effects noted were nephropathy in male rats, and increased liver weights (female rats, male and female mice) at the 9,000 ppm exposure level. A NOAEL of 3,000 ppm (10, 560 mg/m^3) was identified from this study.

Soiefer *et al.* (1991) exposed rats to 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3) commercial hexane for 6 hours a day, 5 days per week for 2 years. No neurobehavioral or neuropathologic effects were observed, and a NOAEL of 9,000 ppm was identified. In a rat study with the same dosing regimen and duration, Kelly *et al.* (1994) reported histological evidence of mucosal irritation in the nasal turbinates and larynx at 9,000 ppm. A NOAEL of 3,000 ppm (10,560 mg/m^3) was identified. This study also evaluated the potential carcinogenicity of commercial hexane and found no evidence of neoplastic effects at any concentration tested.

Table 9 summarizes the subchronic and chronic inhalation NOAELs, LOAELs, and other endpoints that were reported in the animal studies described above.

4.1.4 Developmental and Reproductive Toxicity

No human studies were identified that investigated the reproductive or developmental effects of n-hexane or commercial hexane following inhalation exposure.

There was no evidence of maternal toxicity in pregnant CD rats exposed to 0, 93 or 409 ppm n-hexane (0, 327, or 1,440 mg/m^3) for 6 hours a day during gestational days six to 15 (Litton Bionetics, 1979). There were also no differences in body weight, and all animals appeared normal throughout the study with respect to clinical parameters. There was no observed embryotoxicity or increased incidence of malformations; however, small, statistically insignificant increases in the incidence of subcutaneous haematomas and retarded bone ossification were observed at both test concentrations.

De Martino *et al.* (1987) reported reproductive tissue lesions in male Wistar rats exposed to 5,000 ppm (17,600 mg/m^3) n-hexane for durations up to 6 weeks. The earliest lesions occurred after a single 24-hour treatment and consisted of focal degeneration of primary spermatocytes from the leptotene to the middle pachytene stages, and cytoplasmic swelling of spermatids at late stages of maturation in the testis. Numerous exfoliated and injured germ cells were observed in the epididymis. After cessation of the 24-hour treatment, damage to the seminiferous epithelium increased for the first seven days, and the epididymis showed focal infiltration by inflammatory cells. Recovery was complete within 14 to 30 days post-exposure. More severe lesions were observed in groups treated 16 hours a day for two, four, six or eight consecutive days. After eight days, there was massive exfoliation of apparently normal and degenerated spermatids and spermatocytes at various stages of differentiation. Numerous degenerated spermatocytes were observed. Sertoli cells showed retraction of apical cytoplasm and vacuolization. The lumen of the epididymis contained degenerated spermatids and spermatocytes. Thickening and sclerosis of the arteriolar media was also observed in the interstitium. Five to six weeks of treatment induced a gradual reduction in diameter and collapse of the seminiferous tubules and, in some cases, development of tubules containing only Sertoli cells and rare spermatogonia (aplasia). Numerous lipid droplets were visible in the cytoplasm of Sertoli cells. Testicular damage continued to progress after exposure had ceased.

Table 9 Summary of Subchronic and Chronic n-Hexane Inhalation Toxicology Studies in Experimental Animals

Species	Exposure Period	Air Concentration (mg/m^3)	Reported Effects	Reference
Sprague-Dawley rats	22 h/d for up to 6 months	1,760	Reduced body weight gain	API, 1983a,b
Sprague-Dawley rats	16 h/d for 6 d/wk for 6 wks	17,600	Decreased motor nerve conduction velocity	De Martino *et al.*, 1987
SM-A mice	6 d/wk for 1 year	302, 755, 1510, 3,020 or 6,040 (duration adjusted)	No effects at 302 mg/m^3	Miyagaki, 1967
Sprague-Dawley rats	6 h/d for 5 d/wk for 26 wks and at 21 h/d for 7d/wk for 26 wks	3.8, 16.4 or 81 (duration adjusted) and 15.4, 83 or 389 (duration adjusted)	No pathological signs of nervous system degeneration; NOAEL: 389 mg/m^3	Bio/Dynamics, 1978
B6C3F1 mice	6 h/d for 5 d/wk fro 13 wks or	1,760, 3,520, 14,080 or 35,200	NOAEL: 1,760 mg/m^3 LOAEL: 3,520 mg/m^3	NTP, 1991; Dunnick *et al.*, 1989
	22 h/d for 5 d/wk for 13 wks	3,520		
Charles River rats	22 h/d for 7 d/wk for approximately 6 months	407 to 1,622 (n-hexane or n-hexane plus other hexane isomers)	NOAEL: 407 mg/m^3	IRDC, 1981
Fischer rats	6 h/d for 5 d/wk for 13 wks	1,888, 4,091 or 6,294 (duration adjusted)	NOAEL: 1,888 mg/m^3	Cavender *et al.*, 1984
Fischer 344 rats	24 h/d for 5 d/wk for 11 wks with 6 wk recovery period	1,760, 3,520 or 5,280	NOAEL: 1,760 mg/m^3	Rebert and Sorenson, 1983
Sprague-Dawley rats	9 h/d for 5 d/wk for 14 to 30 wks or 10 h/d for 6 d/wk for 14 to 30 wks	472, 1,416 or 4,721 (duration adjusted) or 3,147 (duration adjusted)	NOAEL: 1,416 mg/m^3 for peripheral neuropathy effects	Frontali *et al.*, 1981
Wistar rats	12 h/d for 7 d/wk for 16 wks	881, 2,115, 5,287 (duration adjusted)	NOAEL(HEC): 881 mg/m^3	Huang *et al.*, 1989
rats and mice	6 h/d for 5 d/wk for 13 wks	3,168, 10,560 or 31,680	NOAEL: 10,560 mg/m^3	Duffy *et al.*, 1991
rats	6 h/d for 5 d/wk for 2 years	3,168, 10,560 or 31,680	NOAEL: 31,680 mg/m^3 for lack of neurobehavioral or neuropathologic effects	Soiefer *et al.*, 1991
rats	6 h/d for 5 d/wk for 2 years	3,168, 10,560 or 31,680	NOAEL: 10,560 mg/m^3	Kelly *et al.*, 1994

In contrast to De Martino *et al.* (1987), Mast *et al.* (1989a) reported no changes in mouse sperm morphology five weeks after exposure to 0, 200, 1,000, or 5,000 ppm (0, 705, 3,525, or 17,624 mg/m^3) ppm n-hexane, 20 hours a day for five days. A concentration of 5,000 ppm also had no effect on the fertility of male mice over an eight-week follow-up period (Mast *et al.*, 1989b). An earlier mouse study also indicated that male mice were less sensitive than rats to n-hexane-induced reproductive effects. Litton Bionetics (1980) reported that the fertility of male CD-1 mice was unaffected by exposure to either 99 (348 mg/m^3) or 396 ppm (1,394 mg/m^3) n-hexane for 6 hours per day, 5 days a week for eight weeks. In addition, fertility indices of females were similar between those mated to controls and treated rats for two weeks following exposure.

Adult male Sprague-Dawley rats were exposed to 0 or 1,000 ppm n-hexane (3,525 mg/m^3; duration-adjusted concentration = 2,644 mg/m^3), as well as 1,000 ppm xylene, or 1,000 ppm n-hexane + 1,000 ppm xylene, for 18 hours a day, seven days per week for 28 or 61 days (Nylen *et al.*, 1989). By two weeks post-exposure, four of six rats had bilateral testicular damage and a reduced body weight. By 10 months post-exposure, three of six rats had bilateral testicular damage and reduced body weight. Testes of the affected rats were markedly reduced in size and weight relative to controls. The muscles of the hind limbs in all rats with testicular damage were severely atrophic. Atrophic changes of seminiferous tubules throughout the testes were also found at two weeks, and 10, 12 and 14 months post-exposure. The testicular tissue of the affected rats showed severe disruption, with total absence of a nerve growth factor-immunoreactive cell population. Total loss of the germ cell line was reported in some rats up to 14 months post-exposure, indicating permanent testicular damage. There was no impairment of androgen synthesis.

In a study where the differential responses of weanling and young adult rats to n-hexane exposure was investigated (Howd *et al.*, 1983), both absolute and relative testes weights were significantly lower in n-hexane-exposed rats relative to controls. Exposure to n-hexane occurred for 24 hours a day, for 11 weeks to up to 1,500 ppm (5,280 mg/m^3) n-hexane. No differences were noted between the two rat age groups.

In pregnant female Wistar rats exposed to 500, 800 or 1,500 ppm (1,760, 2,816, or 5,280 mg/m^3) n-hexane for 23 hours a day throughout the 21 day gestation and lactation period, observed effects included reduced body weight of offspring, reduced maternal weight gain, and increased fetal resorption rates (Stoltenburg-Didinger *et al.*, 1984). Delayed histogenesis of the cerebellar cortex in the offspring also was reported during the first 30 postnatal days. The number of offspring examined in this study was not reported and statistical analysis of body weights was not performed (ATSDR, 1999).

Pregnant albino rats exposed to 0 or 1,000 ppm (3,520 mg/m^3) of 99% n-hexane for six hours a day during gestational days eight to 12, 12 to 16 or 8 to 16 (3 gestational period groups), showed significantly depressed postnatal growth up to three weeks after birth (Bus *et al.*, 1979). This returned to normal by seven weeks post-exposure. No differences in fetal resorption, birth weights, or other abnormalities were noted. There was no

statistically significant difference between the mean litter weights of the exposed and control groups, but a significant transient depression in mean litter weight occurred over the first six weeks post-exposure. A low incidence of enlarged renal pelvis was noted in each of the three treatment groups; however, this only occurred when litters contained fewer than three fetuses. A low, non-significant incidence of misaligned fourth sternebrae also was noted in each of the treatment groups. There were no signs of neuropathy in the pups during a seven-week post-exposure observation period.

Neeper-Bradley (1989a) found that Sprague-Dawley rats exposed to a commercial hexane mixture (53.45% n-hexane) at test concentrations of 0, 914, 3,026 and 9,017 ppm (0, 3,217, 10,651 and 31,740 mg/m^3) did not experience developmental effects. The rats were exposed to the commercial hexane vapour for six hours a day on gestational days six to 15. There were no significant differences between groups with respect to the number of viable implantations per litter, number of nonviable implantations per litter, sex ratio, fetal body weights (total, male and female), incidence of malformations, or incidence of variations. Some maternal toxicity occurred during the exposure period as reduced weight gain, but total weight gain throughout pregnancy was unaffected by exposure. The authors concluded that exposure to commercial hexane vapour by inhalation during organogenesis in Sprague-Dawley rats resulted in maternal toxicity at 3,026 and 9,017 ppm, with no apparent developmental toxicity at any concentration tested. A NOAEL of 914 ppm (3,217 mg/m^3) for maternal toxicity and a NOAEL of 9,017 ppm (31,740 mg/m^3) for developmental toxicity are identified from this study.

In a parallel experiment conducted with CD-1 mice (Neeper-Bradley, 1989b), using the same exposure conditions, there were no significant differences between groups with respect to the number of viable implantations per litter, number of non-viable implantations per litter, sex ratio, or fetal body weights (total, male and female). Slight maternal toxicity (color changes in the lungs at necropsy) was observed at 3,026 and 9,017 ppm (10,651 and 31,740 mg/m^3). A significantly increased incidence of poor ossification occurred in the bilateral bone island at the first lumbar arch and all intermediate phalanges of the hind limb in the 9,017 ppm group. There were no significant differences among groups for incidence of variations. It was concluded that exposure to commercial hexane vapour by inhalation during organogenesis in the CD-1 mice resulted in slight maternal toxicity at 3,026 and 9,017 ppm and slight developmental toxicity at 9,017 ppm. A NOAEL of 914 ppm (3,217 mg/m^3) for maternal toxicity and a LOAEL of 9,017 ppm (31,740 mg/m^3) for developmental toxicity are identified from this study.

NTP (1988), also cited as Mast *et al.* (1988), exposed timed-pregnant (33 females per group) and virgin (10 females per group) Swiss (CD-1) mice to 0, 200, 1,000 and 5,000 ppm (0, 704, 3,520 and 17,600 mg/m^3) of 99.2 % pure n-hexane, for 20 hours a day, for a period of 12 consecutive days during gestation. Plug-positive females were exposed on days 6 to 17 days of gestation. Maternal body weight and total cumulative weight gain for dams in the 5,000 ppm exposure group were significantly reduced relative to controls; however, this was attributed to a reduction in gravid uterine weight, not to a decrease in extragestational gain. Gestational exposure to n-hexane resulted in an increase in the number of resorbed fetuses for all exposure groups relative to the control

group; however, these increases were not concentration-related. Fetal resorption was statistically significant in the 200 ppm group (with respect to early plus late resorptions), and with respect to late resorptions in the 5,000 ppm group. A small, but statistically significant reduction in female (but not male) fetal body weight was observed in the 5,000 ppm group, relative to controls. There were no exposure-related increases for any fetal malformation or variation, nor was there any increase in the incidence of combined malformations or variations. It was concluded that while gestational exposure of CD-1 mice to n-hexane vapours appeared to cause concentration-related developmental toxicity, there was no evidence of teratogenicity. The developmental toxicity was manifested as an increase in the number of resorptions per litter for all exposure levels, and as a decrease in the uterine:extra-gestational weight gain ratio in the 5,000 ppm group. Due to the significant increase in the number of resorptions in the 200 ppm group, a NOAEL was not established in this study.

In a previous study, NTP (1987), also cited as Mast *et al.* (1987), exposed timed-pregnant and virgin Sprague-Dawley rats to 0, 200, 1,000 and 5,000 ppm (0, 704, 3,520 and 17,600 mg/m^3) of 99.9% pure n-hexane, for 20 hours per day for a period of 14 consecutive days during gestation (gestational days 6 to 19). Maternal toxicity occurred as a reduction in extra-gestational maternal weight gain. This was observed in all exposed groups, and was statistically significant for the 5,000 ppm group. Extra-gestational maternal weight gain, relative to controls, was reduced by 20%, 23% and 45% for the 200, 1,000 and 5,000 ppm groups, respectively. Cumulative weight gain for dams in the 1,000 and 5,000 ppm groups was significantly reduced relative to controls by gestational day 20. This also occurred in the 5,000 ppm group by gestational day 13. There were no maternal deaths and no clinical signs of toxicity were noted. Gestational exposure to n-hexane did not result in an increase in the incidence of intrauterine deaths or in the incidence of fetal malformations. There was no effect on the number of implantations, the mean percent of live pups per litter, the mean percent of resorptions per litter, or on the fetal sex ratio when compared to controls. A statistically significant reduction in fetal body weight relative to controls was observed for males in the 1,000 and 5,000 ppm groups (7 and 15% reduction, respectively). Female weights also were reduced in these exposed groups (3 and 14% reduction, respectively), but this was only statistically significant in the 5,000 ppm group. Gravid uterine weight was also significantly less than controls in the 5,000 ppm group. A statistically significant increase in the mean percent incidence per litter of reduced ossification of sternebrae 1-4 was observed in the 5,000 ppm group. This effect correlated positively with exposure concentration. No major abnormalities were observed in any of the fetuses. Variations observed included dilated ureter, renal pelvic cavitation, supernumerary ribs, and reduced skeletal ossifications at several sites. The lowest n-hexane exposure concentration of 200 ppm (704 mg/m^3) was identified as the NOAEL for developmental toxicity.

Daughtrey *et al.* (1994) investigated the toxicity of a commercial hexane mixture (in which n-hexane comprised approximately 53% of the mixture) in mice and rats. In the reproductive toxicity experiment, test animals were exposed to 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3) commercial hexane for six hours a day, five days per week for two generations. No adverse reproductive effects were observed.

The only significant effect noted was reduced body weight gain in the offspring of both generations. Based on this finding, a NOAEL of 3,000 ppm (10,560 mg/m^3) was identified.

Keenan *et al.* (1991) exposed rats and mice to 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3) commercial hexane (containing 53% n-hexane) for six hours a day on the sixth through fifteenth days of gestation. No developmental effects were observed in the offspring of rats or mice at any concentration tested. Maternal toxicity was noted in both species at 3,000 ppm. Based on these findings, a developmental NOAEL of 9,000 ppm (31,680 mg/m^3) was identified and a NOAEL for maternal toxicity of 3,000 ppm (10,560 mg/m^3) was identified.

Marks *et al.* (1980) administered up to 9.9 g/kg/day by gavage to pregnant mice during gestational days six to 15 and observed no teratogenic effects, even at doses above the maximum tolerated dose for the dams. However, a reduction in fetal weight was dose-related at doses of 7.92 and 9.9 g/kg/day although no fetal malformations were observed. Five of 33 dams treated with 9.9 g/kg/day died. According to this study n-hexane was not teratogenic even at maternally toxic doses.

4.1.5 Genotoxicity and Mutagenicity

Genotoxic effects appear to have been rarely evaluated in humans following inhalation exposure to n-hexane. In human lymphocytes, there was no increase in unscheduled DNA synthesis after exposure to 99% pure n-hexane dissolved in 1% dimethylsulfoxide, with or without metabolic activation with rat liver S9 mix. Cytotoxicity was reported at 0.08 and 0.8 mg/ml without S9 (Perocco *et al.*, 1983). Overall, the database on the genotoxic potential of n-hexane is limited and equivocal. In a number of studies, rats appear susceptible to n-hexane-induced genotoxicity, whereas mice appear resistant. Bacterial assays have all shown negative results, and the few Chinese hamster cell line studies have shown mixed results. Further study is needed to determine the significance of these findings for humans.

De Martino *et al.* (1987) reported structural abnormalities in sperm (multinucleated round spermatids and spermatocytes) of Sprague-Dawley rats after exposure to 5,000 ppm (17,600 mg/m^3) n-hexane for 16 hours a day for two to eight days. Similar effects were not observed in mice (Mast *et al.*, 1989a).

In male CD-1 mice exposed to n-hexane at 99 or 396 ppm (348 or 1394 mg/m^3) for six hours a day, five days a week for eight weeks, there were no dominant lethal mutations (Litton Bionetics, 1980). The dominant lethal assay is designed to determine the ability of a test compound to induce genetic damage in the germ cells of treated male mice that could lead to either death or developmental failure of zygotes that are heterozygous for such a lesion (ATSDR, 1999). Similar results were observed in another dominant lethal mutation study in which male Swiss mice were exposed to as much as 5,000 ppm (17,600 mg/m^3) n-hexane, 20 hours a day for five days (Mast *et al.*, 1989b).

No increase was observed in the incidence of micronucleated normochromatic erythrocytes or polychromatic erythrocytes in the peripheral blood of male and female mice exposed to 1,000, 4,000, or 10,000 ppm (3,520, 14,080 or 35,200 mg/m^3) of n-hexane, for six hours a day, five days per week for 13 weeks, or in mice exposed to 1,000 ppm for 22 hours a day for 13 weeks (NTP, 1991).

In bacterial assays, results have generally been negative for n-hexane in strains such as *Escherichia coli, Bacillus subtilis and Salmonella typhimurium,* both with and without metabolic activation (Houk *et al.*, 1989; Ishidate *et al.*, 1984; McCarroll *et al.*, 1981a, b; Mortelmans *et al.*, 1986; Kawachi *et al.*, 1982). NTP (1991) found that n-hexane was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested with a preincubation protocol at doses up to 1,000 µg/plate with or without liver S9 fraction. n-Hexane also tested negative in an *in vitro* test for induction of chromosome loss in *S. cerevisiae* (Mayer and Goin, 1994). However, 2,5-hexanedione was strongly positive in this assay. It was suggested by the authors that this finding was due to an effect of 2,5-hexanedione on microtubule function in the yeast cells, resulting in faulty segregation of chromosomes.

n-Hexane tested negative for sister chromatid exchanges in an *in vivo* mouse bone marrow cytogenetics assay (NTP, 1991). Chromosomal aberrations were slightly increased, but this increase was not significant (NTP, 1991). Treatment at doses up to 5,000 µg/mL in the presence or absence of rat liver S9 did not induce chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells. Sister chromatid exchanges were induced in CHO cells only in the presence of S9, and no dose-response relationship was apparent (NTP, 1991).

There was no evidence of mutagenic activity using n-hexane dissolved in dimethyl sulfoxide in a TK +/- mouse lymphoma (L 5178Y) forward mutation assay, with or without metabolic activation (Hazelton Laboratories, 1981). However, there were problems of cytotoxicity and possible losses of n-hexane by evaporation in this study (WHO, 1991).

In CD rats exposed via inhalation to 528, 1,056 or 2112 mg/m^3 (150, 300 or 600 ppm) n-hexane for six hours a day for five days, there was an increased incidence of bone marrow cells with chromatid breaks at 528 and 1,056 mg/m^3 (Hazelton Laboratories, 1981). Severe chromosomal damage was reported at 2,112 mg/m^3 (600 ppm). In a study using a different batch of n-hexane, an increase in the number of aberrations per cell was reported following exposure to 352 and 1,408 mg/m^3 (100 and 400 ppm).

Lankas *et al.* (1978) conducted a limited investigation of the effect of n-hexane on forward mutation to ouabain resistance in Chinese hamster V79 cells at a plate concentration of 10.34 mg/litre in acetone for two weeks. A negative result was reported, but only one concentration was tested, and in the absence of metabolic activation.

Ishidate and Sofuni (1984) reported chromosomal damage following incubation of a Chinese hamster fibroblast cell line (CHL), without exogenous metabolic activation, with undiluted 95% pure n-hexane at plate concentrations of 66, 198 or 330 µg/ml for 24 or

48 hours. An increase in polyploidy (without structural alteration) was noted after incubation of the cells with of 330 µg/ml for 48 hours.

Egeli *et al.* (2000) found that chromosome aberrations in rat bone marrow cells increased in n-hexane-exposed rats relative to controls. This effect coincided with hematological effects such as decreased hematocrit, hemoglobin concentrations, and mean corpuscular volume, and biochemical effects such as increased conjugated dienes (CD), glutathione (GSH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and catalase (CAT). Histological examinations showed intracytoplasmic vacuolisation, nuclei with lower chromatin, and parenchymatous degenerations in the exposed groups. Microscopy revealed depletion of the erythroid series in bone marrow. The authors concluded that n-hexane appears to be a genotoxic and hematoxic agent leading to degeneration and lipid peroxidation in exposed groups.

4.1.6 Carcinogenicity

No association has been found between the occurrence of cancer in humans and occupational exposure to n-hexane. However, there is currently little information available on the carcinogenic potential of n-hexane in humans; no epidemiological studies were located addressing whether an association exists between occupational n-hexane exposure and cancer (ATSDR, 1999).

Lungarella *et al.* (1984) observed papillary tumours, apparently derived from Clara cells, in the bronchiolar epithelium of New Zealand rabbits exposed to 3,000 ppm (10,560 mg/m^3) n-hexane for eight hours a day, five days a week for 24 weeks. However, this study is limited by its failure to report tumour incidence rates, and the study duration (24 weeks) is insufficient for a cancer bioassay. As such, the validity of these findings is highly questionable.

Daughtrey *et al.* (1994) reported liver tumours in female mice exposed to 9,000 ppm (31,680 mg/m^3) commercial hexane (containing 53% n-hexane) for six hours a day, five days per week for two years. No tumours were observed at the lower tested concentrations of 3,000 and 900 ppm (10,560 and 3,168 mg/m^3), or in controls (0 ppm). A NOAEL of 3,000 ppm (10,560 mg/m^3) was identified. Kelly *et al.* (1994) reported no evidence of neoplastic effects at test concentrations up to 9,000 ppm (31,680 mg/m^3) in rats.

Daughtrey *et al.* (1999) investigated the carcinogenic and chronic toxicity potential of commercial hexane solvent in F344 rats and B6C3F1 mice exposed by inhalation for six hours a day, five days per week for two years. Test concentrations were 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3). There were no significant differences in survivorship between control and exposed groups. The only significant histopathological finding in rats was epithelial cell hyperplasia in the nasoturbinates and larynx of exposed groups. This response was considered to be due to upper respiratory tract tissue irritation. No significant differences in tumour incidence between control and exposed rats were found. In mice, uterine tissue from the 9,000 ppm female group showed a significant decrease in the severity of cystic endometrial hyperplasia, relative to controls. An

increase in the combined incidence of hepatocellular adenomas and carcinomas was observed in 9,000 ppm female mice. The incidence of liver tumours was not significantly increased in the 3,000 ppm or 900 ppm female groups, or in any male exposed group. An increased incidence of pituitary adenomas was observed in female, but not male mice. However, this finding was not considered treatment-related as the incidence in the control group was unusually low, and the incidence in exposed groups within the historical control range. No other treatment-related neoplastic changes were observed in tissues from male or female mice. It was concluded that chronic exposure to commercial hexane solvent at concentrations up to 9,000 ppm (31,680 mg/m^3) was not carcinogenic to F344 rats or to male B6C3F1 mice, but did result in an increased incidence of liver tumours in female B6C3F1 mice.

A similar study was reported by Bio/Dynamics (1995a,b). In B6C3F1 mice (50 per sex per group) exposed to commercial hexane (51.5% n-hexane) at test concentrations of 0, 900, 3,000 and 9,000 ppm (0, 3,168, 10,560 and 31,680 mg/m^3), for six hours a day, five days a week for two years, there was a statistically significant, treatment-related increase in hepatocellular neoplasms (adenoma and carcinoma) in females (Bio/Dynamics, 1995a). Incidences of adenoma were: 4 of 50, 6 of 50, 4 of 50 and 10 of 50 in the 0, 900, 3,000 and 9,000 ppm groups, respectively. Incidences of carcinoma were 3 of 50, 2 of 50, 5 of 50 and 6 of 50, and incidences of total neoplasms were 7 of 50, 8 of 50, 9 of 50 and 16 of 50 in the 0, 900, 3,000 and 9,000 ppm groups, respectively. In males, liver neoplasms were observed but were not treatment-related. There was no treatment-related increase observed for other lesions of the liver. In the 9,000 ppm group, female liver tumour incidence was similar to male controls. A significant treatment-related decrease in severity of cystic endometrial hyperplasia of the uterus was also observed in the 9,000 ppm females. It was suggested that this decrease might indicate a possible treatment-related alteration in the hormonal balance, such as decreased estrogenic stimulation of the uterus, resulting in the female mice displaying the normal incidence of male liver neoplasms. The authors could not determine the components of the hexane mixture that caused the neoplasms. In a parallel study with F344 rats, exposed to the same test concentrations of commercial hexane, there was no increased incidence of neoplasms at any site, in either sex (Bio/Dynamics, 1995b).

Overall, the evidence for carcinogenicity of n-hexane or commercial hexane is limited and inconclusive. Furthermore, the findings are unexpected as rats appear more susceptible than mice to the genotoxic effects of hexane but no tumours were induced in this species by high concentrations of commercial hexane. Mice appear quite resistant to n-hexane genotoxicity; however, female mice displayed an increased incidence of liver tumours. Interestingly, this did not occur in male mice exposed to the same test concentrations.

Few regulatory agencies have classified n-hexane as to its carcinogenicity. The U.S. EPA categorizes n-hexane as "D - not classifiable as to human carcinogenicity", based on a lack of appropriate animal bioassays and human studies. Health Canada, the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have not classified n-hexane for its carcinogenicity.

4.2 Effects on Ecological Receptors

Aquatic Life

Aquatic organisms are relatively tolerant of n-hexane exposure. Sax (1984) reported that >1,000 mg/L is required to kill 50% of exposed "aquatic organisms", but provided no details of species or exposure conditions. In a static test, Bringmann and Kühn (1982) reported an LC50 of >1,000 mg/L in *Daphnia magna*. In general, it unlikely that aquatic organisms in the natural environment would ever be exposed to high concentrations of n-hexane continuously, as this substance is highly volatile and has a low water solubility. Stratton and Smith (1988) reported a 50% reduction in the growth of a culture of the green algae, *Chlorella pyrenoidosa,* in the presence of 2.66% (v/v) hexane. CCME (2000) reports geometric means of the 48 hour LC50 for *Daphnia magna* and the 24 hour LC50 for *Artemia salina* for n-hexane is 3,700 µg/L.

No information was identified on the effects of n-hexane or commercial hexanes on terrestrial invertebrates or plants.

Other Environmental Effects

Based on the available data on the environmental fate, transport and effects of n-hexane, this compound is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns.

Reaction of n-hexane with nitrogen oxides has been found to produce ozone precursors under controlled laboratory conditions (Montgomery, 1991); however, the smog-producing potential of n-hexane is very low relative to other alkanes or chlorinated VOCs (Kopczynski *et al.*, 1972). n-Hexane is considered one of the least photochemically reactive hydrocarbons (Katagiri and Ohashi, 1975).

Summary

In humans, the symptoms of acute n-hexane intoxication following inhalation exposure include: vertigo, dizziness, light-headedness, drowsiness, nausea, headache, eye and throat irritation, and paraesthesia. High intensity short-term exposure to n-hexane, such as that observed with glue sniffers or certain occupational situations may produce severe neuropathy. Symptoms of acute n-hexane toxicity in experimental animals include: various manifestations of neurotoxicity, sensory and motor peripheral neuropathy, as well as respiratory effects and testicular lesions in some studies. Overall, n-hexane appears to be of relatively low acute toxicity in experimental animals. Subchronic and chronic inhalation exposure to n-hexane results primarily in sensory and motor peripheral neuropathy in both humans and experimental animals. Studies with animals also report muscle atrophy, reduced body weights, and respiratory effects in some studies. No human reproductive or developmental studies have been conducted with n-hexane. Animal studies indicate that n-hexane can cause adverse effects in the testicular issue of rats, but not mice. The weight of available evidence suggests that n-hexane does not appear to be

teratogenic or cause serious developmental toxicity. The carcinogenicity evidence for n-hexane is limited and inconclusive. The weight of available evidence from genotoxicity and mutagenicity studies is equivocal. Studies with commercial hexane mixtures all show a lower degree of toxicity than studies with purified n-hexane.

Ongoing Toxicological Research

Based on a review of current and/or ongoing research and/or assessment activities or programs overseen by Health Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME), U.S. National Toxicology Program (NTP), U.S. National Institute of Health CRISP Database, U.S. National Institutes of Environmental Health Sciences (NIEHS), various U.S. EPA offices and programs (*e.g.*, TSCA, Science Advisory Board reports, etc.), Chemical Industries Institute of Toxicology (CIIT), Toxicology Excellence for Risk Assessment (TERA), World Health Organization (WHO), Agency for Toxic Substances and Disease Registry (ATSDR) and Health Effects Institute (HEI), there appear to be a number of current or ongoing studies or reviews related to n-hexane toxicology under the direction of these agencies and institutes. For example, there are a number of ongoing research activities registered in the NIH CRISP (2004) database related to solvent abuse, biomarkers, mechanisms of neurotoxicity, neurotoxic effects, and reproductive and developmental toxicity. The U.S. EPA IRIS database currently indicates that the oral RfD and inhalation RfC for n-hexane are both being reassessed under the IRIS program.

5.0 AMBIENT MONITORING METHODS

This section assesses the various air monitoring methodologies to measure n-hexane in ambient air, and describes their advantages and disadvantages.

5.1 Background

5.1.1 Introduction

Air monitoring is used to determine the concentrations of chemical species in the atmosphere. For any single chemical species, there are typically several methods that can be used, with varying detection levels, sampling periods/frequencies and operational levels-of-effort. Specific air monitoring methods include continuous, integrated passive, grab sampling and integrated active (Lodge, 1988). Many factors must be considered in selecting the best approach based on the overall objectives of the monitoring program. Considerations include minimum detection levels, measurement precision, averaging period and cost.

5.1.2 General Monitoring Approaches

In continuous monitors, a sample of air is drawn past a fast response detector using a pump. The detector produces an electrical signal that is proportional to the concentration of a specific chemical compound. Hourly average concentration information can be recorded by a digital data collection system (*i.e.*, a computer) or other storage medium (chart recorder).

In integrated passive sampling, a reactive surface in a controlled diffusion path is exposed for a nominal period ranging from 24 hours to one month. The reactive surface is analyzed in a chemical laboratory to determine the concentration of the captured compounds. The method is termed passive because pumps are not drawing an air sample past a detector or through a collection medium.

In grab sampling, a whole air sample is collected in a non-reactive steel canister or plastic bag. The air sample is then analyzed in a laboratory to determine the concentration of the compounds in the air sample. Grab samples typically represent samples collected over the course of a few minutes to several hours.

In integrated active sampling, a known volume of air is drawn through a column filled with an absorbent material (for gases) or a collection filter (for particles) using a pump. These absorbent columns or filters are then analyzed in a laboratory to determine the concentrations of the collected compounds. Integrated samples are typically collected once every six days for 24-hours at a time.

Integrated samplers require a sorbent to entrap the chemical species being sampled. The selection of the sorbent will depend on the specific compounds being sampled. Commonly used sorbents include, but are not limited to, Tenax, XAD-2, activated charcoal, Carbotrap C, Anasorb 747, Carbosieve, or a multi-stage combination using

more than one sorbent. Dewulf and Langenhove (1997) describe four criteria that can be used in the selection of an appropriate sorbent. First, it is important that the sampled compounds do not break through the sorbent and that the specific retention volume of the sorbent is known. Secondly, the sorbent cannot influence the sample by causing unwanted reactions with the sample. Thirdly, it is imperative that the sorbent not be contaminated prior to and after the sampling process. Finally, the retention of water on the sorbent should be small to avoid any interference with the laboratory analysis of the sample.

5.1.3 Laboratory Analysis

Collected samples (grab sampling) or sample media (integrated sampling) are analyzed to determine the respective concentrations. The most common process uses a gas chromatograph (GC) coupled to an appropriate detector. The GC process requires the sample to be placed in a heated chamber and purged with inert gas (*e.g.*, helium) to separate and transfer the VOC sample from the sorbent, through a cold trap, onto the front of the GC column, which is initially at a low temperature. The GC column is heated to elute individual compounds based on their retention time (Lodge, 1988). The GC is usually coupled to an appropriate detector. Based on the required specificity and sensitivity of the application, there are several specific and non-specific detectors that can be used.

Non-specific detectors include the nitrogen-phosphorous detector (NPD), the flame ionization detector (FID), the electron capture detector (ECD) and the photo-ionization detector (PID) (U.S. EPA, 1999a). These detectors are generally less costly per analysis than specific detectors and can be more sensitive for specific classes of compounds. For example, if multiple halogenated compounds are targeted, using the ECD would provide more accurate identification. The non-specific detectors are coupled to the GC and individual compounds are identified by their retention time. The downside of using non-specific detectors is that they are prone to greater margins of error since they rely on retention times alone for compound identification. Also, there is a chance that interference can occur due to the presence of non-targeted compounds (U.S. EPA, 1999a).

Specific detectors include the linear quadrupole mass spectrometer (MS) and the ion trap detector. Both of these detectors are mass spectrometers. The mass spectra for individual peaks in the ion chromatogram are analyzed for the fragmented mass patterns of the primary and secondary ions. These fragmentations are compared to known spectra observed under like conditions. Based on the GC retention time and the mass spectral characteristics, each VOC in the sample can be determined.

Mass spectrometry is a more accurate method of determining specific compounds in ambient air samples because of their range of precision and simple identification process. Although the non-specific detectors have some advantages such as lower cost and higher sensitivity, the U.S. EPA (1999b) stresses that mass spectrometry is considered a more definitive identification technique and reduces the chances of misidentification.

5.1.4 Information Sources

Standardized air monitoring methods are documented by the U.S. Environmental Protection Agency (U.S. EPA), the Occupational Safety and Health Administration (OSHA), and the National Institute of Occupational Safety and Health (NIOSH). These agencies provide detailed approaches required to adequately measure hazardous air pollutants (HAPs) in ambient and workplace air using a variety of air monitors and analysis techniques. Other information sources (*e.g.*, technical journals, conference proceedings) were also reviewed to explore other air monitoring technologies, as well as new or emerging technologies.

5.1.4.1 U.S. EPA

The U.S. EPA has developed several air toxics methodologies for sampling VOC in ambient air. Detailed descriptions of these methods are available on the U.S. EPA Technology Transfer Network (TTN) – Ambient Monitoring Technology Information Center (AMTIC). The following U.S. EPA air toxics methods can be used to sample n-hexane:

- Compendium Method TO-15A: Determination of volatile organic compounds in air collected in specially-prepared canisters and analyzed by gas chromatography/mass spectrometry (GC/MS) (U.S. EPA, 1999a).
- Compendium Method TO-17: Determination of volatile organic compounds in ambient air using active sampling onto sorbent tubes (U.S. EPA, 1999b).

The following methods provide alternative monitoring techniques that are specific to point source monitoring:

- Method 0030: Volatile Organic Sampling Train (VOST) (U.S. EPA, 1986).
- Method 0040: Sampling of Principal Organic Hazardous Constituents from Combustion Sources using Tedlar Bags (U.S. EPA, 1996b).

Each of these methodologies can be applied to a range of VOC as determined by previously successful trials conducted by the U.S. EPA. All four methods can be used to sample and analyze n-hexane. The following sections describe each U.S. EPA method.

U.S. EPA Compendium Method TO-15A

Method TO-15A provides procedures for sampling VOC in pressurized (above atmospheric pressure) and subatmospheric pressure canisters. Originally, this method was based on the collection of whole ambient samples using SUMMA passivated stainless steel canisters, but can now be applied to other types of canisters. The set of compounds that can be sampled using the specially prepared canisters is a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act, and includes n-hexane.

This method uses specially prepared canisters with a pump-ventilated sample line for sample collection. For pressurized sampling, an additional pump to pressurize the canister is required. The ambient air sample is drawn through a sampling train, which is made up of components that regulate the rate and length of sampling, into the specially prepared passivated canister. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Compendium Method TO-17

Method TO-17 is a thermal desorption based ambient air monitoring method for VOC and is applicable for 0.5 and 0.25 ppbv ambient concentration levels. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance. These compounds, which are the same as those that can be sampled using TO-15A, are a subset of the 97 VOCs that are listed as hazardous air pollutants in the 1990 amendments of the U.S. Clean Air Act. n-Hexane is among those compounds that can be sampled.

This method uses single or multi-sorbents packed in tubes in order of increasing sorbent strength, allowing for a wide volatility range of VOC to be sampled. Using multi-sorbent tubes, compounds with higher molecular weights are retained first, and compounds with lower molecular weights last. If a single sorbent is being used, it should be specific to the target compound. Because of the specificity of certain sorbents, the thermal desorption process is very efficient.

The sample is drawn through a tube containing the selected sorbents. The n-hexane adsorbs to the sorbents while unwanted VOC and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method 0030

Method 0030 was developed for sampling volatile principal organic hazardous constituents (POHC) from the stack gas effluents of hazardous waste incinerators. Alberta Environment has developed a similar stack sampling code (AENV, 1995), which describes in detail the methods for sampling VOC (method 25) in stack gas effluent. Volatile POHC are compounds with boiling points that are less than 100°C. The U.S. EPA provides a list of compounds for which this method can be used. n-Hexane is among those compounds that can be determined.

This method employs a 20 litre sample stack gas effluent which contains volatile POHC. Using a glass-lined probe and a volatile organic sampling train (VOST), the gas is withdrawn at a rate of 1 L/min. The stream is then cooled to 20°C as it passes through a water-cooled condenser. The volatile POHC are collected on a pair of resin traps. The first trap contains Tenax (poly 2,6-Diphenyl phenylene oxide) sorbent while the second contains a mixture of Tenax and petroleum-based charcoal. Up to six pairs of sorbent traps can be used to collect the volatile POHC over a period of two hours. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

U.S. EPA Method 0040

Method 0040 was developed for sampling and analyzing VOC in gaseous emissions from stationary sources such as hazardous waste incinerators using Tedlar bags. This method is limited to VOC that have a boiling point less than 121°C. A study by Rao *et al.* (1997) conducted in Bombay, India employed Tedlar bags for sampling ambient air at a height of three meters above ground level. This shows the diversity of this sampling technique in that it is not limited to stack sampling. The U.S. EPA provides a list of compounds for which this method can be used based on sampling performance.

This method employs a heated probe and filter through which the sample is drawn before entering a heated three-way valve leading to a condenser where moisture and condensate are removed from the stream to a trap. The VOC are collected in a Tedlar bag that is held in a rigid, air-tight container. The sample is transferred to a laboratory for analysis with a GC coupled to a MS.

5.1.4.2 NIOSH

NIOSH has developed several air toxics methodologies for sampling VOC in workplace air. Detailed descriptions of these methods are contained in the NIOSH Manual of Analytical Methods (NMAM). It should be noted that the NMAM was intended to achieve consistent industrial hygiene analyses and was not designed specifically for ambient air. The following NIOSH analytical method can be used to sample n-hexane:

- NIOSH Manual of Analytical Methods, Fourth Edition, Method 1500: Hydrocarbons, 36 – 126°C BP (NIOSH, 1994).

Method 1500 can be applied to a range of organic compounds including n-hexane. It is a general sampling method and provides a list of compounds that can be determined. The following section describes Method 1500.

NIOSH Method 1500

Method 1500 employs an activated charcoal (prepared from coconut shells) based solid sorbent tube, which is a commonly used sorbent because of its reactive surface which promotes higher adsorptive capacity. It also has a very high area to weight ratio that allows for higher sampling capacity. This method is limited to VOC that have a boiling point between 36 and 126°C. n-Hexane is among those compounds that can be sampled.

The sample is drawn through a tube containing the activated charcoal sorbent. The n-hexane would adsorb to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.1.4.3 OSHA

OSHA has developed several air toxics methodologies for sampling VOCs in ambient air. Detailed descriptions of these methods are available from the Directorate of Science, Technology and Medicine (DSTM): Salt Lake Technical Center (SLTC). It should be noted that these methods were intended to provide a uniform and practical means for evaluating workplace air quality and were not designed specifically for ambient air. The following OSHA analytical methods can be used to sample n-hexane:

- OSHA Sampling and Analytical Methods, Organic Method 7: Organic Vapours (OSHA, 2000).

Organic Method 7 can be applied to a range of organic compounds including n-hexane. It is a general sampling method and provides a list of compounds that can be determined. The following section describes Organic Method 7.

OSHA Method 7

Method 7 is a general organic vapour sampling methodology. It uses an activated charcoal based solid sorbent tube similar to that described in NIOSH Method 1500. Activated charcoal (prepared from coconut shells) is a commonly used sorbent because its reactive surface promotes higher adsorptive capacity. It also has a very high area to weight ratio that allows for higher sampling capacity.

The sample is drawn through a tube containing activated charcoal sorbent. The n-hexane adsorbs to the charcoal sorbent while other highly volatile organic compounds and most inorganic components pass through the tube. The sample is transferred to a laboratory for analysis with a GC coupled to a FID.

5.2 Alternative and Emerging Technologies

The combination of the U.S. EPA, NIOSH, and OSHA ambient air sampling methods provides a broad scope of approaches. The sampling methods described in this section are designed for use over an eight hour to 24 hour period. There are, however, other notable methods of sampling hexane that have been used in the past for specific applications.

Kuo *et al.* (2000) sampled the road-side concentrations of certain VOC including n-hexane in Taichung, Taiwan. Their methodology was a similar approach to U.S. EPA Compendium TO-17, NIOSH method 1501, and OSHA method 7. A small stainless steel tube containing a Carbopack B sorbent and a low-flow sampling pump was attached to the collar of motorists. A GC coupled to a MS was used for analysis of samples.

Uchiyama *et al.* (1999) successfully used a modified diffusion sampler with thermal desorption. The diffusive sampler used either Carboxen or Carbotrap B sorbents to collect VOC through the molecular diffusion and collection. A GC coupled to a MS was used for analysis of samples.

Leibrock and Slemr (1997) conducted a fairly unique, yet effective, sampling technique without the use of a sorbent. Their sampler design employed two cryogenic sampling traps that would remove compounds from the ambient air being drawn into the sampler dependant on their temperature resistance. A GC coupled to a MS was used for analysis of samples.

Environment Canada has used SUMMA canisters based on the U.S. EPA Compendium TO-14A to measure for urban pollutants. This method also has been used in Edmonton, Alberta (Cheng *et al.*, 1997) to measure the concentration of VOC (including n-hexane) in ambient air.

For long-term exposure trends, passive diffusion monitors such 3M 3500 Organic Vapor Monitors have been used. Usually these monitors are exposed for 7 to 24 days and returned to a laboratory for analysis. In a recent animal health study, these monitors were used to measure VOC concentrations in rural Alberta, Saskatchewan and British Columbia.

As new and emerging technologies are developed, agencies such as the U.S. EPA provide information to users ensuring that the best available environmental practices are upheld.

6.0 EXISTING AMBIENT GUIDELINES

Current recommended or proposed n-hexane ambient air quality guidelines from selected regulatory agencies in Canada (other than Alberta), the United States and elsewhere are summarized in Table 10. Appendix A contains further information on each of these existing guidelines.

In general, all jurisdictions reviewed have common uses for their ambient air quality guidelines, including:

- Reviewing permit applications for air emission sources;
- Investigating accidental releases or community complaints about adverse air quality for the purpose of determining follow-up or enforcement activity;
- Conducting health risk assessments of industrial facilities and airsheds; and
- Monitoring and controlling ambient air quality.

The development of ambient air quality guidelines is driven by numerous societal and scientific issues, which require consideration of such factors as aesthetics, property damage, toxicology and ecology. Odour, for example, is an issue of aesthetics, and for chemicals with particularly distasteful odours, guideline values may be driven by odour thresholds, while for airborne chemicals that are corrosive, damage to structures may be a key consideration.

In terms of toxicology, air quality guidelines typically consider basic toxicological principles, which dictate that the response of an organism is a function of the magnitude of the dose and the duration over which the dose is received. The nature of the response of organisms (*i.e.*, the target tissues or organs and the toxicological endpoints) is another important consideration. For example, chemicals that act as primary respiratory irritants may have guidelines developed that are protective of these types of effects. Where toxicity concerns relate to non-respiratory targets (*e.g.*, liver or kidney) or to toxicological endpoints of late onset (*e.g.*, cancer, reproductive), air quality guidelines may be established to be protective of these types of effects. Chemicals that have multiple toxicological endpoints in more than one tissue or organ may have guidelines developed that are protective of the most sensitive toxic effects. Another consideration is the estimated or actual degree of exposure of key receptors to the air pollutant, particularly receptor groups that may exhibit sensitivity to the air pollutant (*e.g.*, elderly, asthmatics, children, *etc.*). Other important considerations in establishing an air quality guideline include the available technologies (and their costs) for routinely or periodically monitoring for the pollutant in air, and the availability and technical feasibility of approaches for estimating ambient ground-level air concentrations, in order to compare to air quality guidelines.

The three most common approaches by which ambient air quality guidelines are developed are as follows:

1. Using an occupational exposure level (OEL) and dividing it by safety or uncertainty factor, and amortizing for continuous exposure. These factors are intended to account for differences between eight-hour exposures in the workplace and continuous 24-hour environmental exposures, increased susceptibility of individuals in the general population *versus* the relatively healthy worker, and uncertainties in the margin of safety provided in an occupational exposure limit. It should be recognized however, that the use of OEL values has its limitations. For example:

    - OELs are based on human effects information in industrial settings and may not accurately reflect ambient environmental exposure situations.
    - OELs are derived to be protective of workers who are typically considered in good health and within the age range of 18 to 65 years. Such individuals are potentially less sensitive and/or susceptible to the effects of airborne pollutants than members of the general population. Among the general populations, there may be subpopulations or individuals that are more sensitive or susceptible to the effects of an airborne pollutant (*e.g.*, elderly, young children, asthmatics, people with pre-existing respiratory conditions, etc.).
    - Worker exposures are typically based on a normal work schedule (eight hours per day, five days per week). For this work schedule, there are two days per week (weekends) in which the body may eliminate much of the accumulated substances before the next workweek begins. However, for individuals continuously exposed to an air pollutant in the ambient environment, there is no similar period of wherein no exposure occurs.

    For these reasons, agencies using OELs as the basis for ambient air quality guidelines typically adjust OELs by applying safety or uncertainty factors.

2. Threshold chemical risk assessment procedures: Used for chemicals that are not believed to act as carcinogens and that exhibit a clear toxicity threshold. In this approach, a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) from a suitable animal or human study is divided by a series of uncertainty factors that account for issues such as: differences between animals and humans, sensitive individuals, use of a LOAEL instead of a NOAEL, and for extrapolation from subchronic to chronic exposure durations.

3. Non-threshold chemical risk assessment procedures: Used for substances believed to act as carcinogens. Cancer potency estimates, slope factors, tumorigenic potency values, etc. are used to establish ambient air levels based on acceptable levels of incremental lifetime cancer risk, such as one in 100,000 in Alberta. These acceptable levels are established by regulatory agencies.

Finally, the potential ecological impact of airborne chemicals also is an important consideration in the guideline-setting process. Although a chemical may have no direct impact on human health or property, transfer of the chemical from the air to the terrestrial and aquatic environments by dry or wet deposition could have ecological impacts, depending on the physical and chemical properties of the substance.

Current occupational exposure limits for n-hexane derived by ACGIH, NIOSH and OSHA are all based on human studies where peripheral neuropathy was the principal effect. Occupational polyneuropathy has been observed at air concentrations as low as 500 ppm (176 mg/m^3) while the minimum level at which n-hexane exhibits neurotoxicity has not been well established (ACGIH, 1998). The current ACGIH Threshold Limit Value – Time Weighted Average (TLV-TWA)[3] and NIOSH Recommended Exposure Limit (REL) values are 50 ppm (176 mg/m^3). The ACGIH TLV also carries a skin designation based on studies showing that peripheral neuropathy can occur following dermal contact with n-hexane (*e.g.*, Nomiyama and Nomiyama, 1974; Nomiyama *et al.*, 1973; Spencer *et al.*, 1980; Spencer and Bischoff, 1987). The ACGIH, NIOSH and OSHA have not established a short-term or ceiling level for n-hexane. The current OSHA Permissible Exposure Level (PEL)-TWA is 500 ppm (1,760 mg/m^3). Although in 1989 OSHA promulgated a PEL-TWA of 50 ppm that would reduce the risk of peripheral neuropathy and other adverse neuropathic effects and by doing so was consistent with the ACGIH TLV-TWA, a 1992 decision by the U.S. Court of Appeals for the Eleventh Circuit overturned this 1989 PEL value (ACGIH, 1998). As a consequence of this decision, n-hexane is regulated by OSHA with a PEL-TWA of 500 ppm (1,760 mg/m^3). ACGIH (1998) reports that occupational exposure limits from other countries are similar to the TLV-TWA. For example, Australia and Germany use a threshold value of 50 ppm (176 mg/m^3). The U.K. uses a value of 20 ppm (70.4 mg/m^3). Germany also uses a short-term level of 100 ppm (352 mg/m^3). Sweden uses an occupational limit of 25 ppm (88 mg/m^3) and a 15-minute short-term value of 50 ppm (176 mg/m^3).

NIOSH (2003) reports an immediately-dangerous-to-life-and-health (IDLH) value of 1,100 ppm (3872 mg/m^3). The IDLH is based strictly on safety considerations and is 10% of the lower explosive limit. Thus, it does not represent an appropriate basis for establishing an ambient air quality guideline.

The U.S. EPA, ATSDR and California EPA Office of Environmental Health Hazard Assessment (OEHHA) have derived health-based airborne ambient exposure levels for n-hexane.

The U.S. EPA (1990) derived an inhalation reference concentration (RfC) of 0.2 mg/m^3. The U.S. EPA identified LOAEL (HEC) values of 73 mg/m^3 (for neurotoxicity) and 77 mg/m^3 (for epithelial nasal lesions), from the Sanagi *et al.* (1980), and Dunnick *et al.* (1989) studies, respectively. A cumulative uncertainty factor of 300 (10-fold to protect sensitive individuals; 10-fold for the use of a LOAEL rather than a NOAEL; 3-fold for lack of data on reproductive and chronic respiratory effects), and a modifying factor or 1.0 was applied to these LOAEL (HEC) values to yield the RfC. The U.S. EPA chose both Sanagi *et al.* (1980) and Dunnick *et al.* (1989) as principal studies. The Sanagi study was chosen as there is considerable evidence that n-hexane is neurotoxic to humans. However, a NOAEL could not be derived from the Sanagi study that identified

[3] TLV-TWA refers to the "time-weighted average concentration for a conventional eight hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effect" (ACGIH 1998)

only a free standing LOAEL. The Dunnick study identified a LOAEL that is very similar to that in the Sanagi study, and also identified a NOAEL based on mild inflammatory lesions of the nasal epithelium. The U.S. EPA assigned a medium confidence rating to the Sanagi *et al.* (1980) study as the LOAEL is based on neurotoxicity, which is supported by numerous other inhalation studies in animals and in human occupational studies. The confidence rating in the database for n-hexane is rated medium because of the lack of long-term inhalation studies and appropriate reproductive studies. Thus, the RfC is assigned a medium confidence rating.

The OEHHA (2003) derived a chronic REL of 7.0 mg/m^3 for n-hexane based on neurotoxicity in animals and electrophysiological alterations in humans. No acute REL was derived by this agency. OEHHA considered three studies relevant to the derivation of a chronic REL (*i.e.,* Miyagaki, 1967; Sanagi *et al.*, 1980; Chang *et al.*, 1993). These studies all evaluated the most sensitive endpoint for n-hexane toxicity (peripheral neuropathy) and involved exposures over a significant fraction of a lifetime. The REL was derived from the NOAEL of 100 ppm (352 mg/m^3) for peripheral neuropathy reported in Miyagaki (1967). This NOAEL was adjusted for exposure duration and converted to a NOAEL (HEC) of 57.9 ppm. A cumulative uncertainty factor of 30 (3-fold for interspecies extrapolation; 10-fold for intraspecies extrapolation) was applied to this NOAEL (HEC) to yield the REL of 7.0 mg/m^3. The OEHHA also derived RELs based on the studies by Sanagi *et al.* (1980) and Chang *et al.* (1993). These RELs were seven to 10-fold lower than the REL of 7.0 mg/m^3 that was derived from Miyagaki (1967). However, it was considered these two human studies likely over-predicted n-hexane risks due to co-exposure to other substances, which are believed to potentiate the effects of n-hexane. As such, OEHHA (2003) considers the current chronic REL of 7.0 mg/m^3 to be adequately protective of human health.

ATSDR (1999) derived a chronic duration inhalation Minimal Risk Level (MRL) of 0.6 ppm (2 mg/m^3) for n-hexane, based on a LOAEL of 58 ppm (204 mg/m^3) for reduced motor nerve conduction velocity in occupationally exposed workers (Sanagi *et al.*, 1980). This LOAEL was adjusted by a factor of 100 (10-fold for use of a LOAEL; 10-fold for human variability) to yield the MRL. It was noted that if the neurotoxicity of n-hexane was potentiated in this study by co-exposure to acetone, the level of n-hexane (alone) required to produce the observed effects would be higher than 58 ppm, and the resulting MRL level would also be higher.

Edwards *et al.* (1996) derived an RfC for commercial hexane of 18.4 mg/m^3. This RfC was based on identified NOAEL values of 3,000 ppm (10,560 mg/m^3) from chronic lifetime exposure studies with rats and mice (*e.g.*, Soiefer *et al.*, 1991; Kelly *et al.*, 1994; Daughtrey *et al.*, 1994). The NOAEL was adjusted for continuous exposure (6/24 x 5/7) and divided by an uncertainty factor of 100 (for animal to human extrapolation and intrahuman variability) to yield the RfC.

For the most part, the guidelines presented in Table 10 are derived based on either the U.S. EPA RfC of 0.2 mg/m^3, or the ACGIH TLV-TWA of 50 ppm (176 mg/m^3) (adjusted with various modifying and uncertainty factors). In the available documentation from

some agencies, the basis behind the air quality guideline is not clearly specified. Further information on the scientific basis for these guidelines, the application of uncertainty factors and the practical application of these guidelines by the respective agencies, is provided in Appendix A.

Table 10 Summary of Existing Air Quality Guidelines for n-hexane

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
California Environmental Protection Agency, Office of Environmental Health Hazard Assessment	Chronic REL (continuous lifetime daily exposure)	7.0	NOAEL of 100 ppm for peripheral neuropathy in rats (Miyagaki, 1967).	2002
Louisiana Department of Environmental Quality	AAS (8 h)	4.2	Basis not provided.	2003
Michigan Department of Environmental Quality	ITSL (24 h)	0.2	U.S. EPA RfC of 0.2 mg/m^3.	2003
Minnesota Department of Health	Chronic HRV (annual average)	2.0	Based on nervous system and upper respiratory effects. HRVs are noted to be derived using best available science and public health policies available at time of development.	2003
Newfoundland and Labrador Department of the Environment	AQS (24 h)	12.0	Basis not provided.	2003
New Hampshire Department of Environmental Services	AAL (24 h)	0.885	ACGIH TLV-TWA of 50 ppm.	1997
	AAL (annual)	0.2	U.S. EPA RfC of 0.2 mg/m^3.	
New Jersey Department of Environmental Protection	RfC (continuous daily exposure)	0.2	U.S. EPA RfC of 0.2 mg/m^3.	2003
New York State Department of Environmental Conservation	AGC (continuous lifetime daily exposure)	0.2	U.S. EPA RfC of 0.2 mg/m^3.	2000
North Carolina Department of Environment and Natural Resources	TAPG (24 h)	1.1	Basis not provided.	2001
Oklahoma Department of Environmental Quality	MAAC (24 h)	17.6	Based on ACGIH TLV-TWA of 50 ppm.	2003

Agency	Name of Guideline (Averaging Period)	Guideline Value (mg/m^3)	Basis of Guideline	Date of Guideline[a]
Ontario Ministry of Environment and Energy	AAQC (24 h)	12.0	Based on health effects but specific scientific basis not provided.	2001
	POI (1/2 h)	35.0	OMOE uses a factor of three to derive ½ h POI standards from AAQC.	
Quebec Ministry of the Environment	MAAQC (continuous lifetime daily exposure)	0.01	U.S. EPA RfC of 0.2 mg/m^3 and adjusted by factor of 5% to account for relative contribution of sources of exposure.	2002
Texas Natural Resource Conservation Commission	Short-term ESL (1 h)	1.8	Basis not provided.	2003
	Long-term ESL (annual)	0.18		
U.S. Agency for Toxic Substances and Disease Registry	Chronic MRL (continuous lifetime daily exposure)	2.0	LOAEL of 58 ppm for reduced motor nerve conduction velocity in occupationally exposed workers (Sanagi *et al.*, 1980).	1999
U.S. Environmental Protection Agency, Integrated Risk Information System (IRIS)	RfC (continuous lifetime daily exposure)	0.2	LOAELs from Sanagi *et al.* (1980), and Dunnick *et al.* (1989) studies. Based on neurotoxicity and electrophysiological alterations in humans.	1990
Vermont Agency of Natural Resources	Short term HAAS (24 h)	4.3	Based on ACGIH TLV-TWA of 50 ppm.	2001
Washington Department of Ecology	ASIL (24 h)	0.2	U.S. EPA RfC of 0.2 mg/m^3.	1998

a Date guideline was either published or date of last review/revision by agency.

The air quality guidelines used by the jurisdictions listed in Table 10 can be split into short-term and long-term values. Short-term ambient air guidelines for n-hexane include half-hour, one-hour, eight-hour and 24-hour averaging periods. Ontario is the only jurisdiction with a half-hour limit (35.0 mg/m^3). A one-hour limit exists in Texas (1.76 mg/m^3). Louisiana cites an eight-hour limit of 4.2 mg/m^3. Twenty-four hour guidelines exist in Michigan, Newfoundland and Labrador, New Hampshire, North Carolina, Oklahoma, Ontario, Vermont and Washington. These 24-hour guideline values range from 0.2 mg/m^3 (Michigan and Washington) to 17.6 mg/m^3 (Oklahoma). Long-term air quality guidelines in the jurisdictions reviewed are generally listed as annual ambient limits or are stipulated for continuous lifetime daily exposure. Such limits exist within California, Minnesota, New Hampshire, New Jersey, New York, Quebec, Texas, ATSDR, and the U.S. EPA. These values range from 0.01 mg/m^3 (Quebec) to 2.0 mg/m^3 (ATSDR and Minnesota).

It should be noted that the considerable variability observed between guidelines is primarily the result of differences in the approaches used for their derivation. While there is generally good agreement with respect to the choice of toxicological studies and data used as the basis for the guidelines, all jurisdictions use different averaging periods and apply unique sets of uncertainty and modifying factors and assumptions in guideline development. The decision to use a particular approach involves policy decisions in addition to scientific considerations.

7.0 DISCUSSION

n-Hexane is not known to be corrosive. While it is highly flammable, this is a safety issue that is separate and distinct from health-based guideline development. The carcinogenicity evidence for n-hexane is equivocal. At present, few regulatory agencies have classified n-hexane as to its carcinogenicity. The U.S. EPA categorizes n-hexane as "D - not classifiable as to human carcinogenicity", based on a lack of appropriate animal bioassays and human studies. Health Canada, The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) have not classified n-hexane for its carcinogenicity. There are no existing air quality guideline values for n-hexane that are based on a carcinogenic endpoint. The weight of available evidence from genotoxicity and mutagenicity studies is equivocal. Based on these considerations, toxicological considerations for n-hexane should focus on non-cancer endpoints for both acute and chronic exposure.

Review of the physical chemical properties (Section 2.0) and the toxicology (Section 4.0) of n-hexane indicate several key benchmark air concentrations that should be considered in establishing an ambient air quality guideline. The odour thresholds for n-hexane are highly variable and have been reported to range from 30 ppm to 248 ppm (106 to 873 mg/m^3) (ACGIH, 1998; Amoore and Hautala, 1983; DHSS, 1997; Verschueren, 1983; van Gemert, 1999).

In humans, the symptoms of acute n-hexane intoxication following inhalation exposure include: vertigo, dizziness, light-headedness, drowsiness, nausea, headache, eye and throat irritation, and paraesthesia. High intensity short-term exposure to n-hexane, such as that observed with glue sniffers or certain occupational situations may produce severe neuropathy. Symptoms of acute n-hexane toxicity in experimental animals include: various manifestations of neurotoxicity, sensory and motor peripheral neuropathy, as well as respiratory effects and testicular lesions in some studies. A number of acute human studies indicate effects from exposure to hexanes in the range of 26 ppm to 25,500 ppm (92 to 89,760 mg/m^3); however, the available acute human studies are few in number, are quite dated, and involved self-reporting of symptoms. Thus, the significance of the reported effects at the low end of this range is questionable. Acute animal studies have demonstrated various adverse effects at concentrations above 2,000 ppm (7,040 mg/m^3). Subchronic and chronic inhalation exposure to n-hexane results primarily in sensory and motor peripheral neuropathy in both humans and experimental animals. Studies with animals also report muscle atrophy, reduced body weights, and respiratory effects in some studies. In human occupational epidemiology studies, peripheral neuropathy has been reported to occur following exposure to a wide range of n-hexane levels in air (ranging from 106 to 8,800 mg/m^3; 30 to 2,500 ppm). In general, it can be estimated that workplace exposure to n-hexane at or above 500 ppm (1,760 mg/m^3) for several months may result in peripheral neuropathy in some individuals (ATSDR, 1999).

Subchronic and chronic animal studies have reported NOAELs in the range of 100 to 3,000 ppm (352 to 10,560 mg/m^3), and LOAELs in the range of 400 to 3,000 ppm (1,408 to 10,560 mg/m^3). No human reproductive or developmental studies have been conducted with n-hexane. Animal studies indicate that n-hexane can cause adverse effects in the testicular tissue of rats, but not mice. Reproductive or developmental toxicity has been reported to occur in rats at n-hexane concentrations >200 to 5,000 ppm (>704 to 17,600 mg/m^3). Commercial hexane studies with rats indicate lower developmental toxicity, with some studies reporting NOAELs between 900 and 3,000 ppm (3,169 and 10,560 mg/m^3) (Neeper-Bradley, 1989a; Daughtrey *et al.*, 1994; Keenan *et al.*, 1991). In mice, which are less sensitive, little or no reproductive or developmental toxicity has been reported at concentrations ranging from 200 to 9,000 ppm (704 to 31,680 mg/m^3). The weight of available evidence suggests that n-hexane does not appear to be teratogenic or cause serious developmental toxicity. Studies with commercial hexane mixtures all show a lower degree of toxicity than studies with purified n-hexane.

All of the short-term guideline values summarized in Table 10 are considerably lower than concentrations of n-hexane or commercial hexane that are reported to result in acute toxicity. Therefore, all these values appear to be adequately protective of human health over their respective averaging periods. All the long-term values in Table 10 are well below the subchronic, chronic and reproductive / developmental NOAEL and LOAEL values reported in the scientific literature. Thus, all the long-term air quality guideline values also appear to be adequately protective of human health.

It should be recognized that most air quality guidelines in Table 10 have the built-in assumption that all human exposure to n-hexane occurs *via* inhalation. They do not account for other sources, pathways and routes of exposure. If exposure were apportioned to reflect these, the values presented in Table 10 would decrease in proportion to the magnitude of the exposure from these other sources, pathways and routes. However, one notable exception to this is the Quebec jurisdiction. The MAAQC for n-hexane in Quebec is based on the U.S. EPA RfC but is adjusted by a factor of 5% to account for the relative contribution of the various sources of exposure (See Appendix A). None of the other jurisdictions reviewed discuss exposure apportionment with respect to n-hexane air quality guidelines in their available documentation.

In addition, none of the agencies with air quality guidelines in Table 10 reported any special consideration of children or other sensitive individuals in air quality guideline development.

Based on the information reviewed, none of the agencies listed in Table 10 specifically acknowledged an ecological component in the development of air quality guidelines for n-hexane.

In addition, given the available data on the environmental fate, transport and effects of n-hexane, n-hexane is not expected to affect the physical properties of the atmosphere, contribute to global warming, deplete stratospheric ozone or alter precipitation patterns. While reaction of n-hexane with nitrogen oxides has been found to produce ozone precursors under controlled laboratory conditions (Montgomery, 1991), the smog-producing potential of n-hexane is considered very low relative to other alkanes or chlorinated VOCs (Kopczynski *et al.*, 1972). n-Hexane is noted to be one of the least photochemically reactive hydrocarbons (Katagiri and Ohashi, 1975).

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APPENDIX A

Review of Air Quality Guidelines for Hexane Used by Agencies in North America and Elsewhere

Agency: California Environmental Protection Agency (Cal EPA), Office of Environmental Health Hazard Assessment (OEHHA)
Guideline Value(s): Chronic reference exposure level (REL) = 7,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: RELs are for use in facility health risk assessments conducted for the AB 2588 Air Toxics "Hot Spots" Program.
Scientific Basis for Guideline Development: The chronic REL was developed from a NOAEL of 100 ppm for nervous system effects in male mice, where the critical effect was peripheral neuropathy. The Cal EPA converted the NOAEL to an average experimental concentration based on the experimental exposure duration and exposure continuity and applied an uncertainty factor of 30 to account for interspecies and intraspecies variation.
Status of Guideline (Date of Last Revision or Update): September 2002.
Additional Comments: n/a
References and Supporting Documentation: California Environmental Protection Agency (Cal EPA). 2002. Chronic Toxicity Summary for n-Hexane. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, September 2002. URL: http://www.oehha.org/air/chronic_rels/AllChrels.html (accessed 11 November 2003).

Agency: Government of Canada.
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Government of Canada. 1996. Health-Based Tolerable Daily Intakes/ Concentrations and Tumorigenic Doses/ Concentrations for Priority Substances. Government of Canada, Health Canada, Environmental Health Directorate, Health Protection Branch. Ottawa, ON. Government of Canada. 1999. Canadian National Ambient Air Quality Objectives (NAAQOs): Process and Status. Government of Canada, Environment Canada, Canadian Council of Ministers of the Environment (CCME). Ontario, Canada. Government of Canada. 2003. Priority Substance Lists (PSLs). Government of Canada, Environment Canada, CEPA Environmental Registry. URL: http://www.ec.gc.ca/CEPARegistry/subs_list/Priority.cfm (accessed 13 November 2003).

Agency: Louisiana Department of Environmental Quality (DEQ).
Guideline Value(s): Ambient air standard (AAS) = 4,190 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Eight-hour averaging time.
Application / How Guideline is Used by Agency: AASs are used by Louisiana DEQ to review permit applications for stationary sources that emit hexane to the atmosphere.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: The Louisiana DEQ classifies n-hexane as an acute and chronic (non-carcinogenic) toxin.
References and Supporting Documentation: Louisiana Department of Environmental Quality (DEQ). 2003. Title 33 Environmental Quality, Part III Air, Chapter 51: Comprehensive Toxic Air Pollutant Emission Control Program. Louisiana Department of Environmental Quality (DEQ). Baton, LA.

Agency: Massachusetts Department of Environmental Protection (DEP).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Massachusetts Department of Environmental Protection (DEP). 1995. Massachusetts Allowable Threshold Concentrations (ATCs). Commonwealth of Massachusetts, Executive Office of Environmental Affairs, Department of Environmental Protection. Boston, MA.

Agency:

Michigan Department of Environmental Quality (DEQ).

Guideline Value(s):

Initial threshold screening level (ITSL) = 200 $\mu g/m^3$.

Averaging Time to Which Guideline Applies:

ITSL = 24-hour averaging time.

Application / How Guideline is Used by Agency:

Michigan air toxic rules require that each source must apply the best available control technology for toxics (T-BACT) and that the emissions of the toxic air contaminant cannot result in a maximum ambient concentration that exceeds the applicable health based screening levels (*i.e.*, ITSL, IRSL, or SRSL). ITSLs are required for any new or modified emissions source or sources for which a permit to install is requested and which emits a toxic air contaminant.

Scientific Basis for Guideline Development:

The ITSL was based on the reference concentration (RfC) of 200 $\mu g/m^3$ for neurotoxicity and electrophysiological alterations established by the U.S. EPA.

Status of Guideline (Date of Last Revision or Update):

n/a

Additional Comments:

The Initial Threshold Screening Level (ITSL) is defined as the health based screening level for non-carcinogenic effects of a toxic air contaminant. It is determined by a number of different methods, depending upon the available toxicological data. The rules specify a hierarchy of methods for determining the ITSL. There are two health based screening levels for carcinogenic effects. These include the Initial Risk Screening Level (IRSL), which is defined as an increased cancer risk of one in one million (10^{-6}), and the Secondary Risk Screening Level (SRSL), which is defined as an increased cancer risk of one in one hundred thousand (10^{-5}). The IRSL applies only to the new or modified source subject to the permit application. If the applicant cannot demonstrate that the emissions of the toxic air contaminant meet the IRSL, they may choose to demonstrate compliance with the SRSL, however in this case they must include all sources of that toxic air contaminant emitted from the plant, not just the emission unit being permitted.

References and Supporting Documentation:

Michigan Department of Environmental Quality (DEQ). 2003. Final Screening Level List. Table 2. Michigan Department of Environmental Quality (DEQ). Air Quality Division. URL: http://www.michigan.gov/deq/0,1607,7-135-3310_4105---,00.html (accessed 12 November 2003).

Michigan Department of Environmental Quality (DEQ). 2002. Procedures for Developing Screening Levels. Michigan Department of Environmental Quality (DEQ). Air Quality Division. Lansing, Michigan.

Agency: Minnesota Department of Health (MDH).
Guideline Value(s): Chronic health risk value (HRV) = 2,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Chronic HRVs are comparable to an annual average concentration of chemicals or defined mixtures of chemicals in air.
Application / How Guideline is Used by Agency: HRVs are used by the MDH and sister agencies such as the Minnesota Pollution Control Agency, to assist in the assessment of potential health risks associated with chemicals in ambient air. HRVs may also be used as one set of criteria for assessing risks in the environmental review process, issuing air permits, risk assessments, and other site-specific assessments.
Scientific Basis for Guideline Development: HRVs were derived using the best peer-reviewed science and public health policies available at the time of their development. Uncertainty values were incorporated to ensure that the HRVs present minimal risk to human health. The chronic HRV specific to n-hexane was based on nervous system and upper respiratory system effects.
Status of Guideline (Date of Last Revision or Update): August 2003.
Additional Comments: The approaches used to develop HRVs are considered conservative (*i.e.*, by design they err in the direction of protecting public health); thus, the MDH is confident that exposures to chemicals in concentrations at or below the HRVs present minimal risk to human health. In addition, because of MDH's conservative approach, exposures to chemical concentrations above HRVs do not necessarily pose a public health risk.
References and Supporting Documentation: Minnesota Department of Health (MDH). 2003. Health Risk Values for Air. Minnesota Department of Health (MDH), Environmental Health in Minnesota. URL: http://www.health.state.mn.us/divs/eh/air/hrvtablepr.htm (accessed 12 November 2003).

Agency: Netherlands Research for Man and Environment (RIVM).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Research for Man and Environment (RIVM). 2001. RIVM Report 711701 025 Re-evaluation of Human-toxicological Maximum Permissible Risk Levels. URL: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf (accessed 13 November 2003).

Agency: Newfoundland and Labrador Air Pollution Control Regulations.
Guideline Value(s): 24-hour air quality standard (AQS) = 12,000 µg/m^3.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: The minister under the Executive Council Act uses the values prescribed in the Criteria for Acceptable Air Quality for controlling air quality, where the amount of air contaminants in the atmosphere due to all sources shall not exceed these values (*i.e.*, AQS).
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): May 2003.
Additional Comments: n/a
References and Supporting Documentation: Newfoundland and Labrador Air Pollution Control Regulations. 2003. Newfoundland and Labrador Regulation 56/03. Government of Newfoundland and Labrador, Queen's Printer, May 2003.

Agency: New Hampshire Department of Environmental Services (DES).
Guideline Value(s): 24-hour ambient air limit (AAL) = 885 $\mu g/m^3$. Annual ambient air limit (AAL) = 200 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AALs are used by the New Hampshire DES to review permit applications for sources that emit n-hexane to the atmosphere. Sources are regulated through a state-wide air permitting system and include any new, modified, or existing stationary source, area source, or device.
Scientific Basis for Guideline Development: The 24-hour AAL is derived from the threshold limit value time weighted average (TLV-TWA) of 50 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. The New Hampshire DES applied a time adjustment factor of 2.8 and a safety factor of 71 to the TLV-TWA. The annual AAL is derived from the reference concentration (RfC) of 200 $\mu g/m^3$ for neurotoxicity and electrophysiological alterations established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): March 1997.
Additional Comments: n/a
References and Supporting Documentation: New Hampshire Department of Environmental Services (DES). New Hampshire Code of Administrative Rules. Chapter Env-A 1400. Regulated Toxic Air Pollutants. New Hampshire Department of Environmental Services (DES). Concord, NH.

Agency: New Jersey Department of Environmental Protection (DEP).
Guideline Value(s): Reference concentration (RfC) = 200 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: RfCs are used by the New Jersey DEP to review permit applications for sources that emit n-hexane to the atmosphere.
Scientific Basis for Guideline Development: The RfC for n-hexane is derived from the reference concentration (RfC) of 200 $\mu g/m^3$ for neurotoxicity and electrophysiological alterations established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): April 2003.
Additional Comments: n/a
References and Supporting Documentation: New Jersey Department of Environmental Protection (DEP). 2003. Reference Concentrations for Short-Term Inhalation Exposure. New Jersey Department of Environmental Protection (DEP), Division of Air Quality, Bureau of Air Quality Evaluation. April, 2003. New Jersey Department of Environmental Protection (DEP). 1994. Technical Manual 1003: Guidance on Preparing a Risk Assessment for Air Contaminant Emissions. New Jersey Department of Environmental Protection (DEP), Air Quality Permitting Program, Bureau of Air Quality Evaluation. Revised December 1994.

Agency: New York State Department of Environmental Conservation (DEC).
Guideline Value(s): Annual guideline concentration (AGC) = 200 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: AGCs are used by the New York State DEC to review permit applications for sources that emit n-hexane to the atmosphere.
Scientific Basis for Guideline Development: The AGC for hexane is derived from the reference concentration (RfC) of 200 $\mu g/m^3$ for neurotoxicity and electrophysiological alterations established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): July 2000.
Additional Comments: n/a
References and Supporting Documentation: New York State Department of Environmental Conservation (DEC). 2000. DAR – 1 AGC/SGC Tables includes TLVs & STELs for the Year 2000. New York State Department of Environmental Conservation, Division of Air Resources, Bureau of Stationary Sources. Albany, NY.

Agency: North Carolina Department of Environment and Natural Resources (DENR).
Guideline Value(s): 24-hour toxic air pollutant guideline (TAPG) = 1.1 mg/m^3 (1,100 $\mu g/m^3$).
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: TAPGs are used by the North Carolina DENR to review permit applications for sources that emit n-hexane to the atmosphere.
Scientific Basis for Guideline Development: Scientific basis was not provided.
Status of Guideline (Date of Last Revision or Update): April 2001.
Additional Comments: n/a
References and Supporting Documentation: North Carolina Department of Environment and Natural Resources (ENR). 2002. North Carolina Air Quality Rules 15A NCAC 2D (Air Pollution Control Requirements) and 15A NCAC 2Q (Air quality Permit Procedures). Section .1100 – Control of Toxic Air Pollutants. North Carolina Department of Environment and Natural Resources. Raleigh, NC.

Agency: Ohio Environmental Protection Agency (EPA)
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: Ohio Environmental Protection Agency (EPA). 2002. Review of New Sources of Air Toxic Emissions. Option A. Ohio Environmental Protection Agency, Division of Air Pollution Control. Columbus, Ohio.

Agency: Oklahoma Department of Environmental Quality (DEQ).
Guideline Value(s): Maximum acceptable ambient air concentration (MAAC) = 17,628 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: MAACs are used by Oklahoma DEQ to review permit applications of sources that emit hexane to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour MAAC was based on the threshold limit value time weighted average (TLV-TWA) of 50 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. A safety factor of 10 was incorporated by the Oklahoma DEQ.
Status of Guideline (Date of Last Revision or Update): November 2003.
Additional Comments: n/a
References and Supporting Documentation: Oklahoma Department of Environmental Quality (DEQ). 2003. Total Air Toxics Partial Listing. Oklahoma Department of Environmental Quality. URL: http://www.deq.state.ok.us/AQDnew/toxics/listings/pollutant_query_1.html (accessed 12 November 2003). Oklahoma Department of Environmental Quality (DEQ). Title 252. Department of Environmental Quality Chapter 100. Air Pollution Control. 100:252-41: Control of Emission of Hazardous and Toxic Air Contaminants. Oklahoma Department of Environmental Quality. Oklahoma City, OK.

Agency: Ontario Ministry of Environment and Energy (OMOE).
Guideline Value(s): 24-hour ambient air quality criteria (AAQC) = 12,000 $\mu g/m^3$. Half-hour point of impingement (POI) = 35,000 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: AAQCs are used by OMOE to represent human health or environmental effect-based values not expected to cause adverse effects based on continuous exposure. AAQCs are not used by OMOE to permit stationary sources that emit hexane into the environment. The 30-minute POI is used by OMOE to review permit applications for stationary sources that emit hexane to the environment.
Scientific Basis for Guideline Development: The AAQC for hexane was derived based on health effects, however the specific scientific basis was not provided. OMOE uses a factor of three to derive half-hour POI standards and guidelines from criteria based on 24-hour averaging concentrations. This factor is derived from empirical measurements, which ensures that if the short-term limit is met, air quality standards based on long-term exposures will not be exceeded.
Status of Guideline (Date of Last Revision or Update): September 2001.
Additional Comments: The half-hour POI is defined as a guideline value by the OMOE.
References and Supporting Documentation: Ontario Ministry of Environment and Energy (OMOE). 2001. Summary of Point of Impingement Standards, Point of Impingement Guidelines, and Ambient Air Quality Criteria (AAQCs). Standards Development Branch, Ontario Ministry of the Environment, September 2001.

Agency: Quebec Ministry of the Environment
Guideline Value(s): Maximum annual air quality criteria (MAAQC) = 10 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: See above.
Application / How Guideline is Used by Agency: MAAQCs are taken into account in the determination of the allowed quantity of a substance in the ambient air and in the exposure received from drinking water, food or other sources.
Scientific Basis for Guideline Development: The MAAQC for n-hexane was based on the reference concentration (RfC) of 0.2 mg/m^3 established by the U.S. EPA. The RfC was adjusted by a factor of 5% to account for the relative contribution of the sources of exposure.
Status of Guideline (Date of Last Revision or Update): May 2002.
Additional Comments: n/a
References and Supporting Documentation: Government of Quebec. 2002. Air Quality Criteria. Government of Quebec, Ministry of the Environment. URL: http://www.menv.gouv.qc.ca/air/criteres/fiches.pdf (accessed 13 November 2003).

Agency: Texas Natural Resource Conservation Commission (TNRCC).
Guideline Value(s): Short-term effects screening level (ESL) = 1,760 µg/m^3. Long-term effects screening level (ESL) = 176 µg/m^3.
Averaging Time to Which Guideline Applies: Short-term ESL = one-hour averaging time. Long-term ESL = annual averaging time.
Application / How Guideline is Used by Agency: ESLs are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. ESLs are based on data concerning health effects, odour nuisance potential, effects with respect to vegetation, and corrosion effects. They are not ambient air standards. If predicted or measured airborne levels of a constituent do not exceed the screening level, adverse health or welfare effects would not be expected to result. If ambient levels of constituents in air exceed the screening levels, it does not necessarily indicate a problem, but rather, triggers a more in-depth review.
Scientific Basis for Guideline Development: The specific scientific basis was not provided for either the short-term or the long-term ESL for n-hexane.
Status of Guideline (Date of Last Revision or Update): October 2003.
Additional Comments: n/a
References and Supporting Documentation: Texas Natural Resource Conservation Commission (TNRCC). 2003. Effects Screening Levels List. URL: http://www.tnrcc.state.tx.us/permitting/tox/esl.html (accessed 13 November 2003).

Agency: U.S. Agency for Toxic Substances and Disease Registry (ATSDR).
Guideline Value(s): Chronic minimum risk level (MRL) = 0.6 ppm (2,112 $\mu g/m^3$).
Averaging Time to Which Guideline Applies: Chronic exposure durations are based on exposure durations equivalent to or greater than 365 days (*i.e.*, one year).
Application / How Guideline is Used by Agency: MRLs are intended to serve as a screening tool to be used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. MRLs are not intended to define clean-up or action levels for ATSDR or other Agencies.
Scientific Basis for Guideline Development: The chronic MRL was based on a LOAEL of 58 ppm for reduced motor nerve conduction velocity in occupationally exposed workers. A safety factor of 100 was applied to the LOAEL by the ATSDR to account for the use of a LOAEL and intraspecies variation.
Status of Guideline (Date of Last Revision or Update): July 1999.
Additional Comments: MRLs are an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects.
References and Supporting Documentation: U.S. Agency for Toxic Substances and Disease Registry (ATSDR). 2003. Toxicological profile for n-hexane. URL: http://www.atsdr.cdc.gov/toxpro2.html (accessed on 11 November 2003).

Agency: U.S. Environmental Protection Agency (EPA).
Guideline Value(s): Reference concentration (RfC) = 200 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: Continuous exposure (daily exposure over a lifetime).
Application / How Guideline is Used by Agency: The RfC was developed for use by the U.S. EPA staff in risk assessments, decision-making, and regulatory activities.
Scientific Basis for Guideline Development: The RfC was developed from a LOAEL of 58 ppm based on neurotoxicity and electrophysiological alterations in an epidemiological inhalation study. The U.S. EPA adjusted the LOAEL from an 8-hour TWA occupational exposure to a continuous environmental exposure and applied an uncertainty factor of 300 to account for unusually sensitive individuals, for the use of a LOAEL rather than a NOAEL, and to account for both the lack of data on reproductive and chronic respiratory effects.
Status of Guideline (Date of Last Revision or Update): 1990.
Additional Comments: The Integrated Risk Information System (IRIS) is an electronic database containing information pertaining to human health effects that may result from environmental exposure to a variety of chemicals. IRIS is prepared and maintained by the U.S. Environmental Protection Agency (EPA).
References and Supporting Documentation: U.S. Environmental Protection Agency (EPA). 2003. Integrated Risk Information System (IRIS). URL: http://www.epa.gov/iris/index.html (accessed 11 November 2003).

Agency: Vermont Agency of Natural Resources (ANR).
Guideline Value(s): Short-term hazardous ambient air standard (HAAS) = 4,290 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: HAASs are used by Vermont ANR to review permit applications for stationary sources that emit n-hexane to the atmosphere.
Scientific Basis for Guideline Development: The short-term HAAS is based on the threshold limit value time weighted average (TLV-TWA) of 50 ppm established by the American Conference of Governmental Industrial Hygienist (ACGIH) as an occupational air standard. Since the n-hexane is associated with both short-term irritant effects and also some type of extended, but not chronic, effect, the Vermont ANR applied a time factor of 4.2 to the TLV-TWA to extrapolate to a continuous level and incorporated a safety factor of 10.
Status of Guideline (Date of Last Revision or Update): November 2001.
Additional Comments: The Vermont ANR classified n-hexane as a non-carcinogen considered to have only short-term irritant effects.
References and Supporting Documentation: Vermont Agency of Natural Resources (ANR). 2001. Air Pollution Control Regulations, Including Amendments to the Regulations Through: November 29, 2001. Vermont Agency of Natural Resources, Air Pollution Control Division, Department of Environmental Conservation, Agency of Natural Resources. Waterbury, Vermont.

Agency: Washington Department of Ecology (DOE).
Guideline Value(s): Acceptable source impact level (ASIL) = 200 $\mu g/m^3$.
Averaging Time to Which Guideline Applies: 24-hour averaging time.
Application / How Guideline is Used by Agency: ASILs are used Washington DOE to review permit applications for stationary sources that emit n-hexane to the atmosphere.
Scientific Basis for Guideline Development: The 24-hour ASIL for n-hexane is derived from the reference concentration (RfC) of 200 $\mu g/m^3$ for neurotoxicity and electrophysiological alterations established by the U.S. EPA.
Status of Guideline (Date of Last Revision or Update): October 1998.
Additional Comments: n/a
References and Supporting Documentation: Washington Department of Ecology (DOE). 1998. Chapter 173-460 WAC. Controls for New Sources of Toxic Air Pollutants. Washington Department of Ecology (DOE). Olympia, WA.

Agency: World Health Organization (WHO).
Guideline Value(s): Does not exist.
Averaging Time to Which Guideline Applies: n/a
Application / How Guideline is Used by Agency: n/a
Scientific Basis for Guideline Development: n/a
Status of Guideline (Date of Last Revision or Update): n/a
Additional Comments: n/a
References and Supporting Documentation: World Health Organization (WHO). 1999. Air Quality Guidelines. Chapter 3: Health-based Guidelines. World Health Organization, Geneva.